USARIEM Technical Report T02-5

ORGANIC CHEMICAL EXPOSURE AND THE RISK OF BREAST CANCER AMONG ACTIVE DUTY WOMEN IN THE U.S. ARMY, 1980-1996

Christopher P. Rennix
Michelle M. Yore
LTC Paul J. Amoroso

Military Performance Division

March 2002

U.S. Army Research Institute of Environmental Medicine
Natick, MA 01760-5007

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. AGENCY USE ONLY *(Leave blank)*	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	October 2001	Technical Report

4. TITLE AND SUBTITLE

Organic Chemical Exposure and the risk of Breast Cancer Among Active Duty Women in the U.S. Army, 1980-1996

5. FUNDING NUMBERS

6. AUTHOR(S)

C.P. Rennix, M.M. Yore, P.J. Amoroso

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

University of Massachusetts, Department of Work Environment
Lowell, Massachusetts, 01854

U.S. Army Research Institute of Environmental Medicine
Natick, Massachusetts, 01760-5007

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Materiel Command
Fort Detrick
Frederick, MD 21702-5012

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

The content of this report was submitted to the Department of Work Environment of the University of Massachusetts in partial fulfillment of the requirements for the degree of Doctor of Science.

12a. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for public release; distribution is unlimited.

12b. DISTRIBUTION CODE

13. ABSTRACT *(Maximum 200 words)*

Young women whose Army occupations involve use of organic solvents may be at particular risk of developing breast cancer. Our objective is to (1) determine if the observed increase in incidence of breast cancer is associated with occupations with high exposure potential for organic solvents, (2) develop job exposure matrices to quantitatively assess the airborne chemical exposure concentrations and cumulative exposure to these chemicals, and (3) investigate the timing of occupational exposure to organic solvents and occurrence of breast cancer. Using the Total Army Injury and Health Outcomes Database, we conducted a cohort study of enlisted active duty Army women. Women whose jobs at diagnosis had a moderate to high exposure potential had a 48% increased risk of breast cancer (95% CI = 1.01-2.07). In a case-control study, parous women who delayed the birth of their first child until after age 25 and had an occupational exposure to formaldehyde had an increased risk (OR 3.2, 95% CI =1.5-6.9). Women 35 years and younger with a family history were also at increased risk (OR 12.0, 95% CI = 4.6-33). The findings support the hypothesis that breast tissue in a proliferative stage may be more susceptible to the effects of occupational exposure to organic solvents.

14. SUBJECT TERMS

Army, TAIHOD, Breast Cancer, Epidemiology, Organic Solvents, Formaldehyde, Case-Control Study, Cohort Study, Military Personnel, Race, Age, Gender, Odds Ratio, Logistic Regression, Alcohol Drinking, Family History, Smoking

15. NUMBER OF PAGES

78

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
UNCLASSIFIED	UNCLASSIFIED	UNCLASSIFIED	UL

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

ACKNOWLEDGMENTS

This report represents the major portion of the first author's dissertation of the same title. It was supported in part by the Commonwealth of Massachusetts Breast Cancer Research Project through the Department of Public Health, the Army Research Institute of Environmental Medicine, and the University of Massachusetts Lowell, Department of Work Environment. The authors would like to thank Drs. Ellen Eisen, Margaret Quinn, and David Wegman of the University of Lowell for their guidance throughout the execution of this research and their comments on the manuscript, and SPC Ty Smith and SPC Andrew Coggins of USARIEM for assistance in data collection at the Veterans Affairs Regional Records Office and the National Archives Records Administration Regional Records Office in St. Louis.

The use of Army records in the preparation of this material is acknowledged, but is not to be construed as implying official Department of Defense approval of the conclusions presented. The views expressed in this report are those of the author and do not reflect the official policy or position of the United States Army Medical Research and Materiel Command, Department of the Army, Department of the Navy, Department of Defense, or the U.S. government. The contents herein are the sole responsibility of the authors and do not necessarily represent the position or policy of the U.S. Army, U.S. Navy, or the Department of Defense. No official endorsement should be inferred.

The author would like to thank the following individuals for their assistance in preparing this technical report:

Laura Senier and Ana Rosas for editing and formatting the report.

Shari Hallas for proofreading the report.

LIST OF ACRONYMS

ACTUR	Automated Central Tumor Registry
ASI	Additional Skill Identifier
CI	confidence interval
CMF	career management field
DMDC	Defense Manpower Data Center
DMOS	duty MOS
DoD	Department of Defense
DOT	Dictionary of Trades
GSD	geometric standard deviation
HHIMS	Health Hazard Information Management System
HRA	Health Risk Appraisal
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
IPDS	Individual Patient Data System
IRR	incidence rate ratio
JEM	job exposure matrix
MHE	material handling equipment
MMA	methyl methacrylate
MOS	Military Occupational Specialty
OEL	occupational exposure limit
OR	odds ratio
PAC	Priority Action Code
PMOS	primary Military Occupational Specialty
ppm	parts per million
ROTC	Reserve Officer Training Corps
SD	standard deviation
SEG	similar exposure groups
SIR	standardized incidence ratio
SQI	Special Qualification Identifier
SSN	Social Security Number
TAIHOD	Total Army Injury and Health Outcomes Database
TDWA	task-duration weighted average
TWA	time weighted averages
VA	Veterans Affairs

EXECUTIVE SUMMARY

Young women whose Army occupations involve use of organic solvents may be at particular risk of developing breast cancer. Our objective is to (1) determine if the observed increase in incidence of breast cancer is associated with occupations with high exposure potential for organic solvents, (2) develop job exposure matrices to quantitatively assess the airborne chemical exposure concentrations and cumulative exposure to these chemicals, and (3) investigate the timing of occupational exposure to organic solvents and occurrence of breast cancer. Using the Total Army Injury and Health Outcomes Database, we conducted a cohort study of enlisted active duty Army women. Women whose jobs at diagnosis had a moderate to high exposure potential had a 48% increased risk of breast cancer (95% CI = 1.01-2.07). In a case-control study, parous women who delayed the birth of their first child until after age 25 and had an occupational exposure to formaldehyde had an increased risk (OR 3.2, 95% CI =1.5-6.9). Women 35 years and younger with a family history were also at increased risk (OR 12.0, 95% CI = 4.6-33). The findings support the hypothesis that breast tissue in a proliferative stage may be more susceptible to the effects of occupational exposure to organic solvents.

CHAPTER 1: INCIDENCE OF OCCUPATIONAL BREAST CANCER AMONG ACTIVE DUTY WOMEN IN THE U.S. ARMY

INTRODUCTION

In 1973, women in the U.S. Army became eligible for assignment into more than 100 occupational specialties that had previously been closed to them, including industrial jobs such as auto mechanics, aviation ground equipment support, and motor transport operators. Before implementation of the all-volunteer force policy in 1973, women were restricted to health care and administrative occupations and comprised less than 2% of the total force. By 1996, women accounted for more than 12% of the total Army force. As in the general U.S. population, the incidence of invasive breast cancer among women in the Army has increased steadily between 1980 and 1996, with the most dramatic increase occurring since 1988. This coincides with the changes in the occupational structure of the Army that allowed women to be assigned to all occupations except those related to direct combat. Early general population studies of female breast cancer and occupation either ignored cases from the military or grouped them in one occupation entitled Armed Forces. Results of recent occupational studies of the general population have been limited due to insufficient sample size or exposure information for specific occupations.

The objective of this study was to investigate, via a retrospective cohort study, the risk of breast cancer among active duty Army women by occupation, with a particular focus on exposure to organic solvents. This was done using newly available Army population and exposure data from various agencies within the Department of Defense and Army that describe a cohort of active duty women in the Army from 1980-1996.

BACKGROUND

Occupational Classification in the Army

The Army has a two-tiered labor structure (14). Industrial, skilled, and unskilled laborers are generally assigned occupations in the enlisted ranks, while professional and leadership positions are grouped similarly in the officer ranks. Occupations within the Army are assigned based on several factors including scores on aptitude, medical, and physical capability tests, the skills and desires of the member, level of formal education, and the operational needs of the Army.

Enlisted personnel generally enter the Army sometime after they complete high school and may enlist as young as 17 years of age with parental permission. Enlisted members are assigned an initial Military Occupational Specialty (MOS) at the time they sign their enlistment contracts. The MOS is a broad occupational classification that identifies groups of skills without regard to levels of skill and is analogous to a job title, as defined in the U.S. Census Codes, for the civilian sector. A list of tasks and skills associated with a particular MOS, Light Wheel Vehicle Mechanic (63B), appears in Appendix B. All enlisted members complete an intense six-week training period for

general military skills and follow-up at trade schools for their assigned MOS area. Upon successful completion of this initial training, a soldier is assigned a primary Military Occupational Specialty (PMOS). If a member completes additional training in another occupation, they are assigned a secondary MOS. All jobs within the Army are coded using the MOS, the minimal level of experience, and any subspecialties unique to the situation. The aspects of the MOS are contained within the MOS code system. For example, a physical therapy technician position at a hospital might be coded as 91B10N9:

91B is the MOS for a medical specialist (Dictionary of Trades occupational title: Emergency Medical Technician; all medical specialists receive initial training to provide basic medical support in combat situations). The '91' is the career management field (CMF) for medical MOSs. The CMF is used to group related MOSs such as health care, food services, and administration.

1 (fourth character) is the skill and grade level indicating an entry-level position. This variable ranges from 0 (no prior experience or working towards initial award of the MOS) to 5 (senior enlisted management).

0 (fifth character) is the Special Qualification Identifier (SQI) which, in this case, indicates that special skill qualifications are not required. There are 19 possible SQI codes, two of which are closed to women (i.e., Ranger, or special combat forces, and Ranger-Parachutist).

N9 (sixth and seventh character) comprise the Additional Skill Identifier (ASI) which, in this case, indicates that additional skill training in physical therapy is required. There are more than 100 ASI codes.

Officers are divided into two categories: commissioned and warrant. A commissioned officer typically has a degree from a four-year college and leadership or professional skills in a specific area, and enters the service sometime after the age of 21 or 22 years. The main sources of commissioned officers are through the military academies, Officer Candidate Schools, Reserve Officer Training Corps (ROTC), and direct appointments (for professionals such as physicians, nurses, lawyers, and members of the clergy). Warrant officers comprise a very small percentage of the total Army population, and are either selected for promotion from the enlisted ranks based upon their enlisted experience or enter the Army as warrant officers directly because they have significant civilian experience in a trade or skill. Officers are assigned positions using the same system of codes as enlisted personnel.

The main purpose of this highly structured occupational scheme is to provide a stable pool of trained workers, capable of moving to a new location on short notice and providing the same set of skills, expertise, and leadership required for the position. The workers are trained to be interchangeable within job classification (MOS) from one location to another. The success of this policy depends upon maintaining a sufficient number of workers in each MOS and limiting MOS changes to special circumstances.

The consistency in job activities and work practices across locations combined with the fact that military personnel tend to stay in the same job aided the occupational analyses described in this report.

Military employment policies differ from those in the civilian sector in two respects: age of hire and retirement. Except for a limited number of professions (i.e., clergy and physicians), the statutory limit for entry into the Army or transfer from the enlisted to the officer corps is 35 years of age. A person can or may be forced to retire from the Army after they complete 20 years of active service. Once a person has attained eight to ten years of service in the Army, they are likely to remain in the service until they can retire. It is very common for a military member as young as 38-40 years of age to retire with full medical and health benefits. This means that the population of women studied in this report is largely premenopausal.

Ultimately, what a person is trained and qualified to do and what they actually do depends upon the needs of the unit commander and the specific unit mission. Due to personnel shortages or emergent mission requirements, workers may be assigned to virtually any job within the unit. Workers in this situation are given a duty MOS (DMOS). Primary and duty MOS assignments are tracked by periodic, Army-wide personnel reports, at least annually, to provide a snapshot of the staffing levels throughout the Army. If a person is assigned a job that is not his or her primary MOS, a duty MOS is entered into the personnel record. For the purpose of this study, the duty MOS was used to code occupation because it best represented the type of work and potential occupational exposures required by the job. If the duty MOS was not completed in the personnel record, the primary MOS was used.

Risk Factors for Breast Cancer

Breast Development. The prevention of breast cancer in women is centered around the current understanding of breast tissue development and carcinogenesis. The mammary glands are among the only organs not fully developed at birth (49). Before menarche, the glands consist mostly of undifferentiated, highly proliferative Type 1 lobules, usually in clusters of 6-11 ductules per lobule. At the onset of puberty, the Type 1 lobules begin to differentiate to Type 2 lobules, continuing until about age 25 or an earlier full-term pregnancy. Under continued hormone stimulation by estrogen and progesterone, especially during pregnancy, Type 2 lobules will differentiate to Type 3 lobules with an average of 80 ductules or alveoli per lobule. If a woman has a full-term pregnancy, Type 4 lobules complete the evolutionary process and the glands can lactate. In nulliparous women, with or without a diagnosis of breast cancer, Type 1 lobules dominate the breast, comprising 60% of the structures, followed by Type 2 (25%-30%), and Type 3 (10%-15%). Parous women with no history of breast cancer have a much lower Type 1 lobule percentage (25%), higher Type 2 lobules (35%), and mostly Type 3 (40%). It has been observed that parous women with a diagnosis of breast cancer have a breast architecture similar to nulliparous women, indicating that their pregnancy failed to promote the development of Types 3 and 4 lobules (49). Lobule Types 3 and 4 are considered relatively refractory to carcinogenesis due to their fully differentiated state and are considered protective until menopause. At menopause,

the lobules begin an involutionary phase, with the proportion of Type 1 lobules once again predominating the breast tissue. The Type 1 lobules in nulliparous women appear to be biologically different from those of parous women because nulliparous menopausal women have a higher incidence of intraductal breast cancer than parous menopausal women (48).

During the early stages of breast development, the rate of cell replication is accelerated, peaking at age 25 years and declining until about 35 years of age or first full-term pregnancy, increasing the probability of genetic errors. Except for exposure to a few chemicals and ionizing radiation, the cause and time of initiation of the cancer process is unknown in breast tissue. Kuller (25) proposed that all women have precancerous lesions in their breasts and, as seen in much of the work with tumor suppressor genes BRCA and p53, the fate of these lesions depends upon the body's ability to repair or destroy these mutations or to prevent them from developing further into tumors. Defects in these and other tumor suppressor genes have been detected in about 10% of diagnosed breast cancers (12, 38).

The likelihood that the incidence of breast cancer can be reduced is illustrated by the variation in breast cancer rates throughout the world. The timing of exposure to exogenous agents during development of female mammary tissue appears to be related to breast cancer risk. When women move from areas with low incidence of breast cancer to areas with higher incidence, their risk rises to that of the host area within two generations, indicating some environmental or lifestyle risk factors that may be controllable (28, 38). The age at which a woman migrates to the new area is an additional factor to consider. In several studies, women who migrated after age 24 from an area with lower breast cancer incidence rates than those observed in the new area did not have a significant increase in their risk, while those who were less than age 24 at migration had an elevated risk (4, 28).

Age. The age at which a woman experiences certain reproductive events is an important indicator of risk for breast cancer. These events are indicative of the changes in and the duration of breast tissue exposure to hormones, especially estrogen. Figure 1 illustrates the average timeline for breast tissue development and includes pathways for parous and nulliparous women. It is a synthesis of findings and proposed biologic mechanisms by Kuller (25), Lipworth (28), and Russo and Russo (47-49). The initiation of breast tissue development normally precedes menarche by two years. Menarche represents the approximate beginning of endogenous estrogen exposure in women. The next significant reproductive event is the first full-term pregnancy. For parous women, risk estimates for breast cancer are significantly reduced for women who gave birth before age 25 (8, 25, 28, 49, 58, 60, 61), but elevated in those who had their first child after age 30 (37). Perimenopause begins at around 35 years of age when a gradual reduction in estrogen levels begins until the ovaries cease production and menopause begins. A woman's lifetime exposure to estrogen is typically measured as the time between menarche and menopause and may be adjusted for pregnancies, births, and bilateral oophorectomy (25, 37, 60). Several studies found increased risk for breast cancer in women whose age at menarche was less than 12 or 13 years old. Women with later onset of menopause, greater than 55 years or older, were reported in

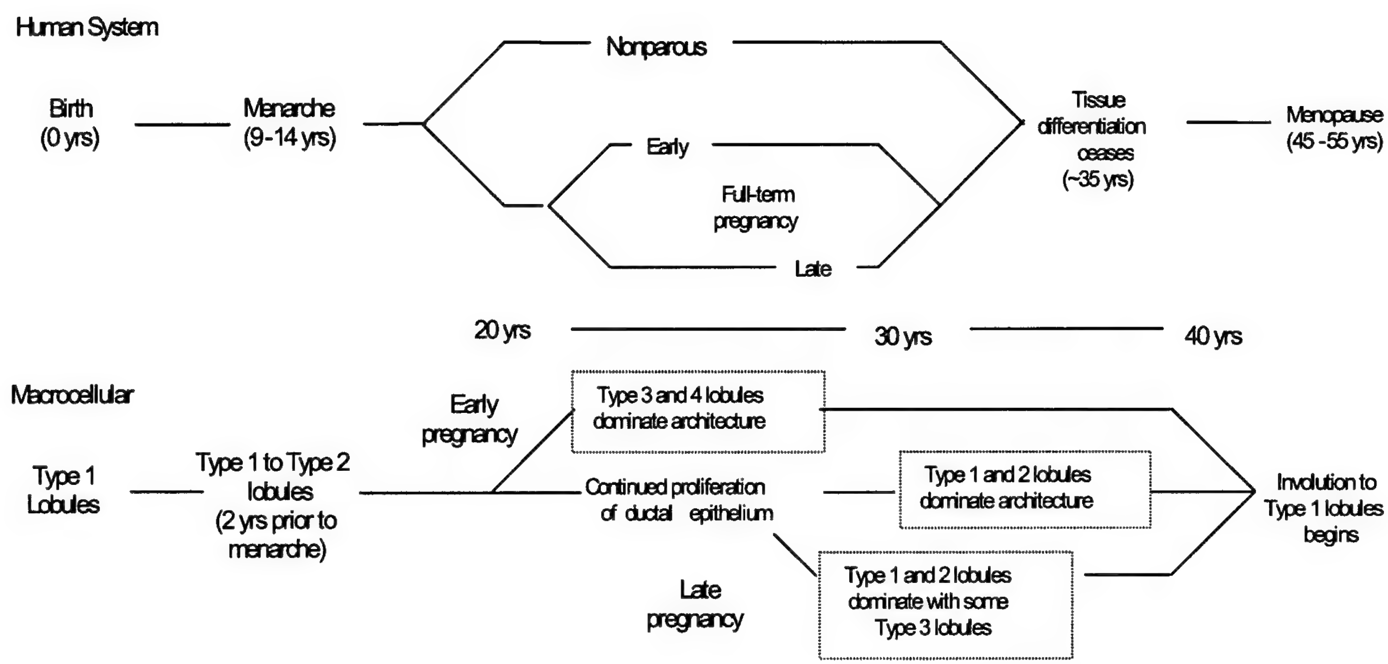
several studies to have a two-fold risk when compared to those less than 46 years at menopause (28).

Race. The role race plays in the incidence of breast cancer is not completely understood. In the U.S., the incidence of breast cancer in black women is higher than in white women from 20-40 years, with the difference decreasing with increasing age. From age 40, a higher incidence rate is observed for white women. Women of Asian origin have the lowest lifetime incidence rates, followed by black, Hawaiian, and white women (33). In an attempt to explain the differences in breast cancer risk seen among racial groups, socioeconomic status has been proposed as an indicator of access to health care, assuming that poorer women have limited access to primary health care. Thus far, studies have reported a positive association between higher socioeconomic status and breast cancer risk within racial groups (7, 21, 29). The difference in incidence rates appears to be more attributable to socioeconomic status and recognized risk factors such as delayed childbirth and fewer births than for race alone (7). Other explanations for the racial difference in breast cancer incidence include genetic susceptibility, P-450 metabolism variations, and diet.

Family History of Breast Cancer. A history of breast cancer in a first degree relative is significantly associated with an increased risk for breast cancer, especially in cases that occur before the age of 30 years (9). Two studies that investigated breast cancer in women aged 45 years and younger reported a positive history of familial breast cancer in 11% and 32% of the cases (57, 61). This strong association led to a research focus on the genetic causes of breast cancer and the subsequent understanding of the role the BRCA1, BRCA2, and p53 genes play in tumor suppression. Mutations in these specific genes are found in up to 10% of all breast cancer cases and women, with the BRCA1 mutation having an 85% increased risk (5).

Occupation. In general, occupation, including exposure to chemicals and environmental agents, and the duration and chronology of employment, provides important exposure information that may be associated with an increased risk for disease or injury. It is interesting to note that breast cancer was first associated with an occupation, nuns, by Ramazzini more than 200 years ago (11). While estrogen was not an occupational chemical used by the nuns, their vocation required those lifestyle choices that increased their risk. It is difficult to find a sufficiently large employed population with detailed health histories and workplace monitoring for specific chemicals and physical agents that goes far enough back in time to allow an appropriate analysis for cancer risk. This is especially true for women. In a 1996 review of occupational risk factors for female breast cancer, Goldberg and Labrèche concluded that few studies provided detailed occupational histories, limiting the quantitative assessment of exposure (16). The most obvious reasons for the small number of occupational exposure studies to date for breast cancer include low statistical power due to the relatively small number of women in chemically exposed manufacturing occupations, the use of broad occupational classifications to represent exposure, and a limited number of comprehensive chemical exposure and health records.

Figure 1. Development of Breast Tissue in Women



Alcohol. Several studies found an elevated risk in women with a recent history of alcohol consumption before a first diagnosis of breast cancer (6, 32, 55, 57). Several mechanisms have been proposed that would establish alcohol as a late stage tumor promoter (19, 22, 57). The relative risks for these studies ranged from 1.2-2.4 for recent consumption of two drinks or more per day (19, 31, 61). Alcohol is metabolized in the body through the P-450 enzyme system, mostly in the liver. Several studies have shown that the P-450 enzyme system can be easily saturated, allowing unmetabolized alcohol to circulate longer in the blood stream. Breast tissue has an incomplete repertoire of P-450 enzymes, incompletely metabolizing the alcohol, exposing the tissue to more metabolic intermediates including acetaldehyde (22, 30).

Organic Solvents and Other Organic Chemicals. Organic solvents are lipophilic and are readily stored in the adipose tissue of the breast and other organs. Because the breast has limited metabolic capabilities, the solvents may persist in the breast, and those that are metabolized may become more toxic due to the lack of detoxifying enzymes. The mammary glands secrete fluids that appear to be recycled through the lymphatic system via the breast ductal system. Organic solvents (and other lipophilic substances) have been found in breast fluid at higher concentrations than those found in the plasma, indicating that the selective reabsorption of the fluid may concentrate these exogenous compounds in the breast ductal structures. LaBrèche and Goldberg (26) proposed that the bioaccumulated solvents and their metabolites have an extended contact time with the ductal cells and may initiate or promote carcinogenesis. The metabolic pathways for the breakdown of organic solvents involve many of the same enzymes as those used for alcohol metabolism. Solvent metabolism that occurs in breast tissue cells may cause an accumulation of epoxides, free radicals, or alkylating agents, because the cells lack enzymes critical to the detoxification pathway. Solvents are suspected to be late-stage promoters for breast cancer. Organic solvents used on the job may behave as xenoestrogens or carcinogens, interacting structurally and dynamically with the female endocrine system and the cellular processes of breast tissue development. LaBrèche and Goldberg (26) hypothesized that organic solvents act directly as genotoxic agents or indirectly through their metabolites on the breast ductal parenchyma. The organic solvents and chemicals selected for this examination (Table 1) were listed as probable or suspected breast carcinogens in the literature (17, 26, 57).

Table 1. Study Organic Solvents and Chemicals for Cohort Study

Chlorinated hydrocarbons	
	Methylene chloride
	Trichloroethylene
	1,1,1-Trichloroethane
	1,1-Dichloroethane
	Perchloroethylene
Aromatics	
	Benzene
	Gasoline and other blended aromatic solvents
	Aviation fuels
	Styrene
Alcohols, aldehydes, and ketones	
	Methyl ethyl ketone
	Formaldehyde (with methanol)
	Glutaraldehyde
	Methanol
	Ethanol
	Isopropanol
Blended solvents (aliphatic and aromatic)	
	Paint solvents
	Gasoline and other blended aromatic solvents
	Aviation fuels

METHODS

Cohort Definition

The study cohort examined was identified using the personnel record database of the Total Army Injury and Health Outcomes Database (TAIHOD) for all active duty Army women from 1 January 1980 to 31 December 1996 (2, 3). The database is a census that is collected at least annually and includes personal, demographic, and occupational information. Because of privacy issues, the Social Security Number (SSN) is encrypted for all records. More detailed information on the personnel variables in the TAIHOD appears in Appendix A. Women who entered and left the Army between two consecutive census dates were not included in the study because their time in service would be less than one year, and their occupational status could not be determined. Also, records with obvious input errors (e.g., age less than 17) that could not be corrected using other available databases were excluded. Person-time was calculated from the date of entry on active duty and end of active service for women who left the Army before the end of follow-up or 31 December 1996, whichever came first.

Case Definition

Cases of invasive breast cancer among women on active duty at the time of their diagnosis were identified from two databases: hospital admissions and histopathology records. Because of privacy restrictions on using the TAIHOD database, cases of invasive breast cancer among cohort members who were not on active duty at the time of their diagnosis could not be determined. Cases admitted to military medical treatment facilities are reported in the portion of TAIHOD that included the Individual Patient Data System (IPDS), a database used by the Army to manage, plan, and implement health care policy. The IPDS includes fields for the primary diagnosis at admission, up to seven secondary diagnoses, and basic demographic information. The IPDS diagnosis fields were searched to identify the first occurrence of malignant breast cancer during the study period for admission to the hospital for invasive breast cancer using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) number, 174. The other source for identifying cases was the Automated Central Tumor Registry (ACTUR), a Department of Defense managed database. The ACTUR database has a diagnosis field for the histologic classification of the tumor. The follow-up period was selected because 1 January 1980 was the first complete year of the hospitalization database, and 31 December 1996 was selected to ensure that all medical treatment facility records could be identified and were included. Collection of hospitalization information from the facilities, data checking and cleaning, and preparation for distribution took up to six months to complete. Case diagnosis was confirmed using the ACTUR, medical record review, or hospitalization and surgical reports. Specific case information was available for some of the cases including cancer type and stage, tumor size and number, treatment course, estrogen and progesterone receptor status, personal and family cancer histories, and alcohol and tobacco use histories.

Obtaining Risk Factor Information

Demographic, reproductive, and lifestyle risk factors were collected from reviews of the personnel database in TAIHOD, Army health records, and the Army Health Risk Appraisal (HRA) database in TAIHOD. Army health records were not used as the sole source for risk factor information because it was not routinely collected, the collection method was not standardized, and the records were not computerized. Each time a woman received a physical exam, a health history was collected on a standard form that was focused on personal illness, injury, and hospitalization. Prior to the mid-1970s, the form included family histories for cancer, menarche, smoking status, and alcohol use. These questions were dropped from the subsequent versions of the form. The health record review was conducted at the Veterans Affairs Regional Records Office and the National Archives Records Administration Regional Records Office, both in St. Louis, MO. Army health records were archived according to the date of discharge or retirement from active service. The National Archives Regional Records office was the custodian of health records for women who left the Army before October 1992. The Veterans Affairs Regional Records Office was responsible for the remainder of the health records and for those women who filed for Veterans Affairs (VA) benefits after

leaving the Army. A request for VA benefits required the health record to be transferred to the VA regional office where the request was processed.

Risk factor data were abstracted on a form designed for this study. It included age at menarche, age at birth of first child, family history of breast cancer, body mass index, chemical sensitivity, and alcohol and tobacco use history. The HRA is a voluntary questionnaire used since 1987 to collect health and lifestyle information and to provide an individualized risk appraisal to each respondent. Army members are offered the HRA at numerous times, usually at medical treatment encounters, and many soldiers complete it more than once. Because the HRA is a voluntary instrument, it may not be completed equally by all members and at all locations throughout the world. HRA surveys used in this study were from the cohort members, though they may have taken the survey as late as 1998.

Occupational Classification (MOS)

There are more than 600 separate enlisted and 600 commissioned and warrant officer MOSs. As described earlier, an MOS comprises a group of similar occupational tasks. Because the Army must maintain a pool of similarly trained workers, those with the same MOS perform the same tasks and use the same chemicals in the workplace. Determination of the MOS for the women in the study was based on the MOS at the time of the annual census. For this study, the duty MOS was the first choice of the assigned work because it represented the actual occupation at the time of the census. If the duty MOS field was empty, indicating that the worker was assigned a job using the primary MOS, then the primary MOS was used. The secondary MOS was not used because it is an additional occupational qualification and does not represent an assigned job.

The number of job changes for each cohort member was determined by using the job held at the time of her initial annual census compared to the jobs listed on subsequent censuses. MOS codes for students were ignored because a student MOS indicated that the member was attending school for the present MOS or for a new MOS. To determine if a member changed career fields when she changed jobs, the CMF was used.

The Defense Manpower Data Center (DMDC) provided conversion tables to relate MOS to the 1970 Bureau of the Census occupational classification scheme. The Department of Defense has a broader occupational classification scheme, similar to the first digit of the Dictionary of Trades (DOT) occupational classification system, which uses nine enlisted and ten officer categories. Census occupational titles were used when Army occupations were compared to civilian job titles in the Results section.

Analysis

Age-adjusted standardized incidence rates and ratios for female breast cancer were computed for specific occupations using these age groups: 17-19 years, 20-24 years, 25-29 years, 30-34 years, 35-39 years, 40-44 years, and 45-65 years.

To investigate the solvent hypothesis of LeBreche and Goldberg (26) and other organic chemicals, two categories of the potential for exposure to organic chemicals were created based on workplace evaluations conducted by Army industrial hygienists. Beginning in 1988, the Army used a standardized rating system to assign risk and potential for exposure and to set priorities to workplaces for further exposure prevention action. The ratings for exposure potential were "none," "low," "moderate," and "high." For this study, MOSs that were assessed at least once with moderate or high potential for organic chemical exposure were grouped as ever "exposed" and all others as "unexposed."

All standardized incidence ratios were calculated using the cohort as the standard population. Person-years were calculated from personnel records for the cohort. Incidence rates per 100,000 person-years were applied to the age distribution of individuals in each occupational category to obtain expected numbers. Poisson regression was conducted in STATA version 5 (STATA Corporation, College Station, TX) to evaluate the association between working in jobs with a moderate or high exposure potential and breast cancer. The datasets used in the analysis contained the number of person-years and number of cases by exposure category and nonexposure covariates: age at risk (intervals given above), race (black, white, other), and year of diagnosis (1980-1983, 1984-1988, 1989-1992, 1993-1996). Incidence rate ratios and confidence intervals were calculated using the Poisson regression procedure.

RESULTS

Cohort Definition

The cohort included 305,048 women who were identified as active duty on any of the annual censuses from 1980-1996, comprising about 10.7% of the total Army.

Case Definition

There were 280 cases of invasive breast cancer identified through the hospitalization database in TAIHOD. When matched to the personnel database in TAIHOD, 40 cases were removed due to misclassification of duty status (misclassified as "active" instead of "reserve") and three were not listed in the TAIHOD personnel database at all (probably due to an incorrect SSN in the hospitalization database), leaving 237 cases who met the case definition. The duty status of the cases was verified using the active and reserve personnel databases from TAIHOD. An additional 35 cases were identified through the tumor registry after comparison with the TAIHOD personnel database to ascertain the case duty status. By locating these 35 tumor registry cases in the TAIHOD hospitalization database, it was found that 17 cases were initially admitted for benign breast disease, and the hospitalization database was not updated to indicate the results of the pathology report. Because the hospitalization database is limited to hospital admissions, the remaining 18 cases with positive pathology for invasive breast cancer were not recorded in the database because the cases did not receive their initial diagnosis at military medical facilities, or they were

treated without admission to the hospital. Thus, the pathology reports for these 35 cases were recorded only through the tumor registry system.

Risk Factors

Risk factor information for the cohort was obtained from the TAIHOD personnel database (age, race, and occupation) and the HRA database (menarche, age at birth of first child, family history of breast cancer, and smoking and alcohol use histories). The risk factors from the personnel database were available for more than 98% of the cohort, and the HRA provided additional risk factor information for about 54,000 study members or 18% of the cohort.

Age. The Army has a relatively young work force, as illustrated in Table 2. Initial periods of enlistment for women are for three to six years, with an average length of employment of 4.2 years. More than 97% of the female warrant officers had prior enlisted experience, increasing the overall mean age of warrant officers to 34.6 years. Officers tended to be older than enlisted members because most had completed college before receiving their commission and some of the officers have prior enlisted experience, increasing their mean age at entry into the Army as officers.

Length of Service. While the Army is a young work force, it is also an aging work force. Since 1973, when recruitment for the all volunteer force began, the number of women who remained beyond the first enlistment period has steadily increased, raising the mean length of employment for all pay grades from three years in 1980 to its peak of 6.7 years in 1995 (slope of the regression line, $p < 0.001$). The mean length of employment for the cohort was 4.5 years. Because women who entered the Army after 1991 may have contracts that go beyond the end of the study period, the mean length of employment for the entire cohort is lower than if members could leave the Army at any time. When the cohort was limited to those who exited the Army before the end of follow-up, the mean length of employment increases from 4.5 to 5.1 years. The mean length of time among active duty cases from first entry into the Army and the initial diagnosis of breast cancer is 12.3 years, with 49% of the cases occurring with less than 13 years of active service (Figure 2).

Race. Minorities account for about 43% of the total cohort (Table 2). Figure 3 illustrates the change in the racial and ethnic makeup of the Army, using white and minority person-time over the study period. The person-time for minority women grew at a rate of 539 person-years per year, while the person-time for white women fell at a rate of 605 person-years per year over the same period ($p < 0.01$).

The Army has had a very aggressive Equal Employment Opportunity policy in force since the mid-1980s, attracting and retaining more minorities, leading to a higher proportion of minorities in the present Army than in the general working population. Race is classified in several of the source databases for the present study, ranging from four to seven subgroups. It is Army policy that the service member selects her race from the list that always includes "Other." When comparing the race designation for the same individuals across databases, it was found that race was selected differently

about 8% of the time. This may be accounted for by the lack of distinction within some choices in the personnel database and several choices in the other databases (i.e., whites or other in the personnel database may include some Hispanics in the other databases).

Menarche. Mean age at menarche among cohort members who completed the HRA was 12.9 years old (Table 3). The mean age at menarche decreased from 13.1 years old for those who completed the HRA survey in 1989 to 12.8 for those who completed the survey in 1997, the last year for which we have complete HRA information for women in the cohort. The rate of change in the mean age at menarche was statistically significant ($p = 0.01$) over the nine years of the survey. Recall bias was explored because the mean age of the women taking the HRA survey was 27 years old, and there was a concern that the women in the study may had difficulty recalling their age at menarche when it occurred about 14 years before. Of the 54,000 women who took the survey, 9,925 took the survey more than once, and the difference in reported age at menarche was investigated. More than 60% (6,019) had no difference, 29% had a difference of one year, and 7% had a two-year difference. The mean age at menarche was not significantly different between the first and last surveys, 13.2 and 13.1, respectively. Statistically significant differences were observed when comparing age at menarche or parity between ethnic groups, but the difference between the age of menarche for the youngest and oldest groups was less than 2.4 months. When a person had more than one HRA survey in the database, the last one was used for the analysis. It is more likely that a member had more information about the survey and provided more accurate responses in the latest survey. Other reasons for discrepant reports may have been caused by the definition of menarche. The survey did not provide a definition beyond first menstrual period, leaving the respondent to determine if this meant first time blood was observed, first full menses, or first regular period. Also, when the surveys are issued en masse at accession points and during troop evolutions, questions concerning specific definitions are less likely to be asked than when administered in a health clinic.

Age at Birth of First Child. The mean age of the women at the birth of their first child ranged from 21.4–22.2 between 1989–1997, with an overall mean age of 21.9 years. Ninety-five percent gave birth to their first child before the age of 30. More than one-half of the women who took the survey were nulliparous. Differences for age at birth of first child grouped by race were statistically significant. Black women had the lowest mean age at 21.4 years, followed by American Indian/Alaskan (21.7 years), Hispanic (21.8 years), White (22.7 years), and Asian/Pacific Islander (23.4 years).

Table 2. Demographic and Occupational Factors for Cases and Cohort, U.S. Army Women, 1980-1996

	Cases[a]				Cohort			
	Enlisted	Officer		Total	Enlisted	Officer		Total
		Warrant	Commissioned			Warrant	Commissioned	
Number	184 (68%)[b]	3 (1%)	85 (31%)	272	274,596 (90%)	1,173 (<1%)	29,279(10%)	305,048
Mean age at entry	23.1 (4.7)[c]	19.3 (2.3)	28.1 (7.5)	24.5 (6.1)	20.3 (0.2)	25.3 (6.2)	23.9 (0.7)	20.6 (3.6)
Mean age at diagnosis	34.4 (6.7)	37.3 (2.3)	41.1 (7.6)	36.3 (7.6)				
Mean length of service (years)	11.1 (5.9)	13.2 (--)	13.3 (7.4)	11.8 (6.4)	4.2 (1.1)	12.5 (2.8)	7.7 (1.6)	4.5 (4.3)
Mean age at exit[d]					24.8 (1.3)	34.6 (2.6)	31.6 (1.8)	25.4 (5.7)
Race								
White	64 (52%)[b]	2 (1%)	58 (47%)	124	151,996 (87%)	766 (<1%)	21,873(13%)	174,605
Black	105 (83%)	1 (1%)	20 (16%)	126	100,092 (95%)	305 (<1%)	5,122 (5%)	105,519
Hispanic	4 (67%)	0	2 (33%)	6	9,473 (92%)	38 (<1%)	745 (7%)	10,256
Asian/Pacific Islander	6 (55%)	0	5 (45%)	11	4,259 (84%)	21 (<1%)	771 (15%)	5,051
American Indian/Alaskan Native	0	0	0	0	2,155 (94%)	8 (<1%)	722 (5%)	2,285
Other	5 (100%)	0	0	5	6,418 (92%)	26 (<1%)	544 (8%)	6,988
Total	**184**	**3**	**85**	**272**	**274,393**	**1,164**	**29,147**	**304,704**[e]

a - Women diagnosed with invasive breast cancer while still on active duty
b - Percentage of row total
c - Standard deviation
d - Only those who left before the end of follow-up (31 DEC 96) are included
e - 344 women did not have race designated.

Figure 2. Breast Cancer Cases Among Active Duty Army Women, by Years Since First Hire, 1980-1996

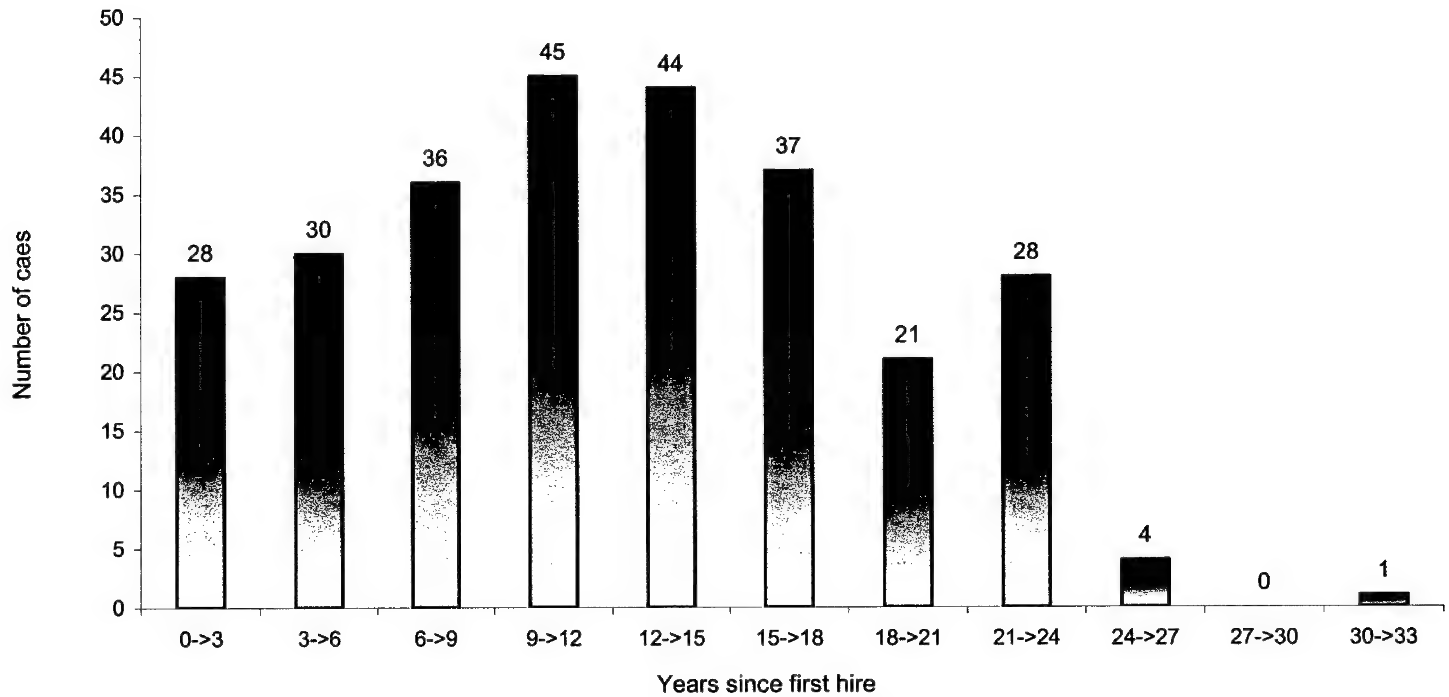


Figure 3. Person-Time by Whites and Minorities, U.S. Army Women, 1980-1996

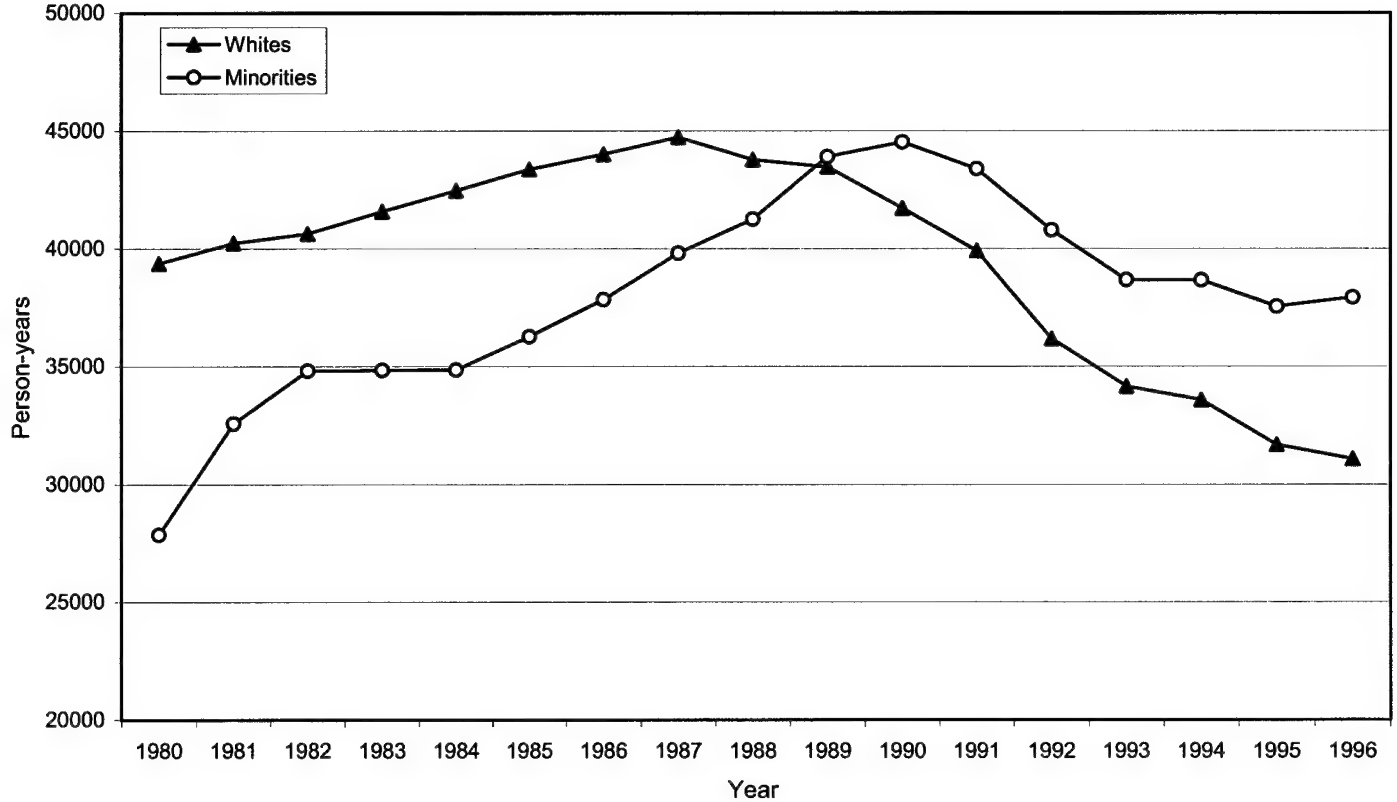


Table 3. Mean and Quintile Values for Age at Menarche, at Birth of First Child, and at Time of HRA Survey, U.S. Army Women, 1989-1996

Parity	Number of Respondents[a]	Age at Menarche	Age at birth of first child	Mean age at survey
Parous	22,947	12.8 (12, 14)[b]	21.9 (19, 24)	29.9 (24, 35)
Nulliparous	30,845	12.9 (12, 14)		24.7 (20, 27)
All	53,792	12.9 (12, 14)		26.9 (21, 31)

a - Not all respondents submitted complete questionnaires
b - 25% and 75% quintile values

Family History of Breast Cancer. Of the 48,000 women who responded to the question in the HRA on family history of breast cancer (88% of total cohort), 9.0% reported having one or more primary relatives with breast cancer. This was most common among white women, with 9.7% reporting a positive family history, and least common among Asian/Pacific Islanders, with 7.4% reporting positive family history. Approximately 10% of parous women (9.5%) reported a positive family history, compared with 8.8% of nulliparous women. These results are similar to the 10.7% reported in a case-control study of breast cancer among women in the general population under the age of 45 (8).

Alcohol Consumption. Forty percent of more than 52,000 women who completed the HRA reported consuming more than 1 alcoholic drink per week, and 4.4% reported consuming more than six drinks per week. The drinking rate across several age strata ranged from 24% for women aged 17-19 years to 44% among women aged 25-29 and 45-49 years. Female officers had a higher positive response for drinking alcohol (51%) than female enlisted members (38%). Blacks reported a drinking rate of 31%, lower than whites at 49%. Several alcohol and breast cancer studies reported drinking rates ("ever/never" or "current status in drinks per day") greater than those observed in the Army, ranging from 63.5% to 90.4% (6, 19, 30, 57).

Occupational Factors

Occupational Classification (MOS). There are more than 600 separate enlisted and 600 commissioned and warrant officer occupational classifications (MOSs) for both men and women in the Army. In recent years, women have moved into occupations formerly closed to women in significant numbers. Of the top 21 enlisted MOSs, only Light Wheel Vehicle Mechanic (corresponding Census title: Auto Mechanic) comprised fewer than 10% women (Table 4). Job choice is affected by the restriction for women on combat-related occupations, career progression, range of occupational training, and those occupations that have a high percentage of billets in combat units. A billet is a job that is defined using the MOS and skill and experience identifiers. The number of women in these billets is restricted because the men need a noncombat billet to which they can transfer when their time in the combat unit is completed. There were six Army occupations that employed a higher percentage of women than comparable occupations in the civilian sector (36): Military Police, Medical Equipment Repairer,

Motor Transport Operator, Petroleum Supply Specialist, Multichannel Transmission System Operator-Maintainer, and Light Wheel Vehicle Mechanic.

Table 4. Distribution of Enlisted Personnel Among the Top 21 Job Titles, Enlisted Army Women, 1980-1996

Military Occupational Specialty	Census Job Title	Female (%)[a]
Automated Logistical Specialist	Traffic/Ship/Receive Clerk	32,444 (21.3)
Administrative Specialist	Administrative Assistant	30,875 (40.0)
Medical Specialist	Health Technician, NEC[b]	13,712 (22.4)
Food Service Specialist	Cook	13,712 (22.4)
Military Police	Police/Detective (Public Servant)	12,026 (13.0)[c]
Motor Transport Operator	Truck Driver	9,970 (12.5)[c]
Record Telecommunications Operator	Data Entry -- Keyers	9,474 (31.5)
Medical Equipment Repairer	Special Mechanic/Repairer NEC	6,989 (23.8)[c]
Personnel Management Specialist	Personnel Clerk (except Payroll)	6,958 (25.9)
Petroleum Supply Specialist	Special Mechanic/Repairer NEC	6,419 (19.1)[c]
Light Wheel Vehicle Mechanic	Auto Mechanic	6,280 (7.6)[c]
Multichannel Transmission System Operator-Maintainer	Electrical Repair/Communications	6,141 (14.4)[c]
Radio Operator-Maintainer	Broadcast Equipment Operator	5,022 (11.9)
Practical Nurse	LP Nurse	4,873 (35.5)
Personnel Records Specialist	Personnel Clerk (except Payroll)	4,309 (36.4)
Finance Spec	Payroll Clerk	4,150 (33.5)
Medical Laboratory Spec	Health Technician	3,712 (41.5)
Dental Specialist	Dental Assistant	3,337 (38.4)
Information System Operator/Analyst	Computer Operator	3,267 (27.1)
Chemical Operations Specialist	Technician, NEC	2,574 (10.1)

a - Percentage women in job
b - Not Elsewhere Classified
c - Exceeds 1997 Bureau of Labor Statistics

An important factor in assessing risk due to occupational exposures is the length of employment in each job. Using the first assigned MOS as the initial job, 81% of enlisted women with more than one year of active service kept the same job throughout their Army career and 15% changed job titles at least once (Table 5). Female officers had more job changes than enlisted women. Forty four percent of women had the same job throughout their career as officers, 33% held two, and 13% had three MOS changes. This can be partially explained by the officer classification scheme. While a medical specialist, an enlisted job title, has a variety of duties and tasks described by a single MOS, a Nurse Corps Officer may have three or four MOS designations based upon her assignment within the hospital (i.e., medical surgical, clinical, operating room, and nurse administrator), provided she has the qualifications to work in these areas. Changing job titles in the officer ranks is part of normal career progression. Many of the job changes occurred within the same CMF, with 88% of enlisted and 74% of officers remaining within their CMF during their career. For example, a medical specialist, MOS 91B, may acquire new skills and become a practical nurse, 91C. The consistency in

MOS assignment in the enlisted population means that the specific exposures tend not to change, but the degree of these exposures may change. Army women did not change jobs very often, and this makes accurate exposure assessments easier.

Table 5. Changes in MOS and Career Management Fields (CMF) for Enlisted and Officers, U.S. Army Women, 1980-1996

	Enlisted	Officers
Mean length of time in all MOSs, in years (SD[a])	4.2 (3.0)	3.3 (2.7)
Mean length of time for those with only one MOS in their career, in years (SD)	4.5 (2.8)	4.8 (3.1)
Number of MOS changes in career:		
% with only one job	80.8	43.8
% with two jobs	5.3	33.2
% with three jobs	3.0	13.2
% with four or more jobs	0.9	9.8
Number of CMF changes in career:		
% with jobs within same CMF	88.3	73.8
% with jobs in two CMFs	10.0	17.8
% with jobs in three CMFs	1.3	5.8
% with jobs in four or more CMFs	0.4	2.6

a - Standard Deviation

The mean length of time in the same job for enlisted women was 4.5 years and, for those who changed jobs, the mean was 4.2 years. This indicates that most enlisted women leave the Army after their first enlistment period. Officers change jobs more frequently, and their mean time in any MOS is much lower (3.2 years). For those officers who stayed in the same job throughout their entire tour in the Army, the mean was 4.8 years.

Breast Cancer Incidence

Incidence of Breast Cancer. The overall age-adjusted incidence rate for breast cancer increased significantly over time from 17 cases per 100,000 person years in 1985-1988 to a high of 24 cases per 100,000 person years in 1993-1996 (Figure 4, $p < 0.05$). Figure 4 shows a 44% decrease in the incidence rate for women 40 years of age and older and the increases among women 17-29 years (almost threefold) and 30-39 years (70%) over the study period. Table 2 includes a summary of cases by pay grade and race.

Race. The overall standardized incidence rate for enlisted blacks (1.13) was higher than for enlisted whites (1.00), though the difference was not statistically significant. When the age-adjusted rates were compared over time, the rate of increase for each group was the same (Figure 5), with blacks always higher than whites.

Figure 4. Standardized Incidence Rates for Breast Cancer, by Year of Diagnosis, U.S. Army Women, 1980-1996

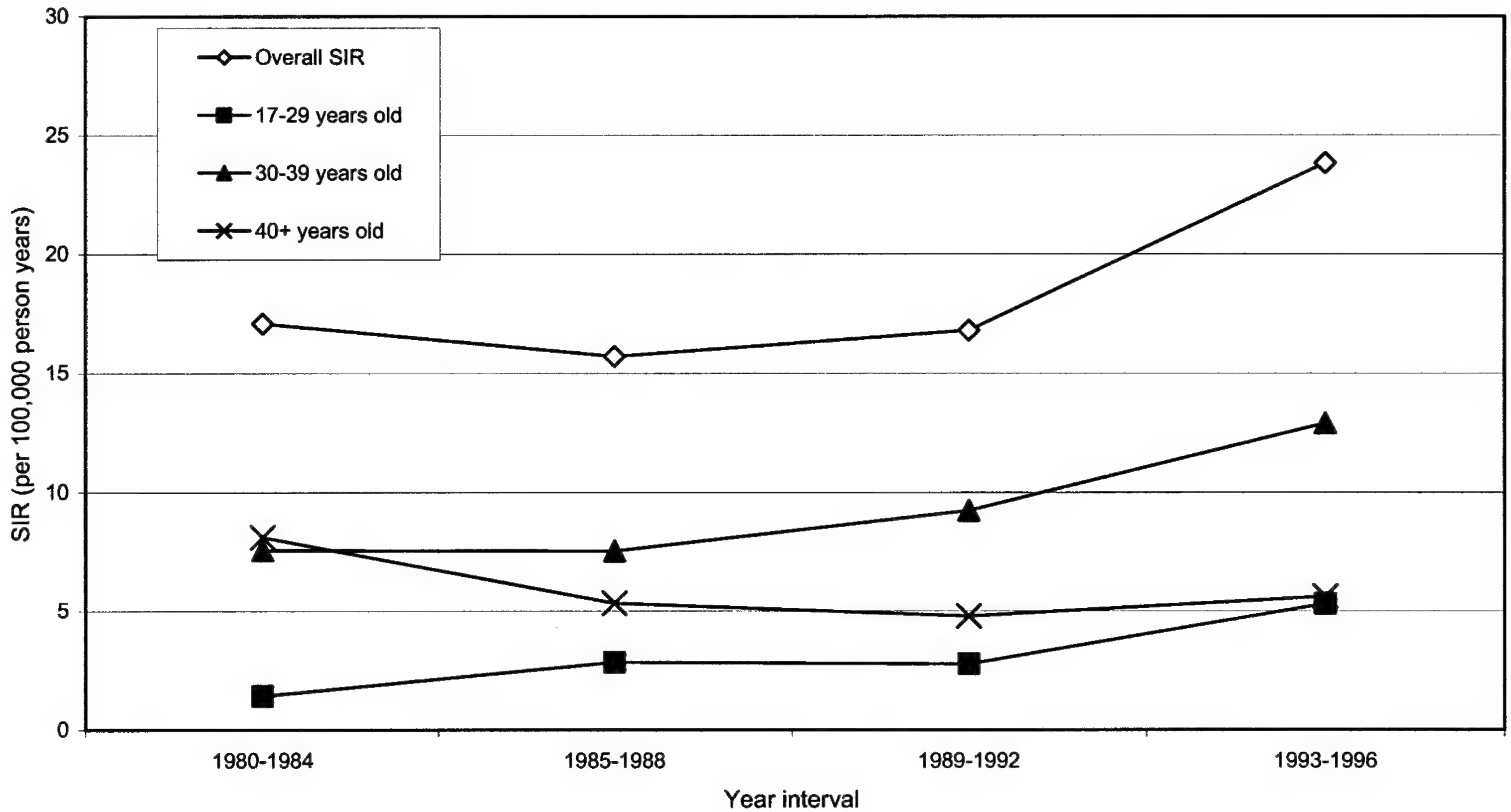
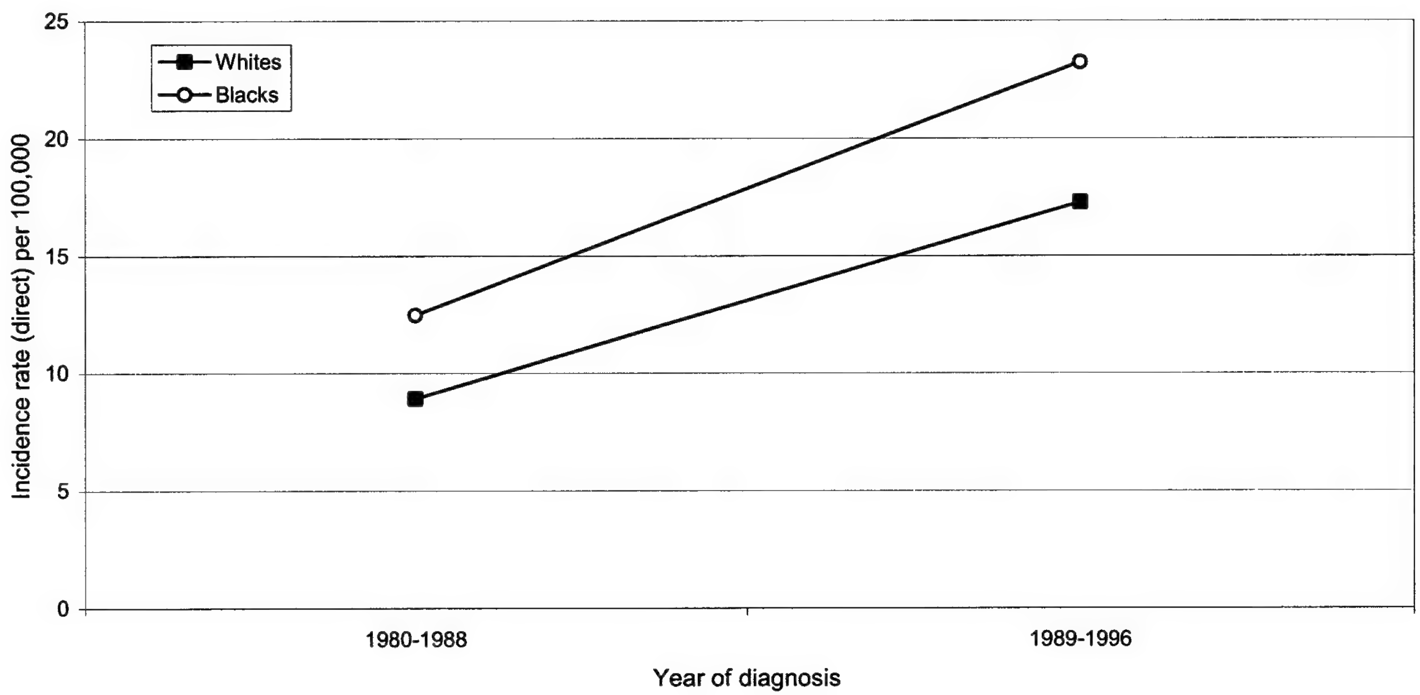


Figure 5. Standardized Incidence Rates for Enlisted Women, by Race, U.S. Army, 1980-1996



Occupation. The 272 breast cancer cases were distributed over 63 enlisted (N=184) and 42 (N=88) officer jobs at the time of diagnosis. The first analysis of occupation among enlisted women was limited to the top 21 jobs (MOSs or occupational classifications) in order to provide sufficient numbers to keep the age-adjusted rates as stable as possible (Table 6). None of the incidence ratios for "job at the time of first diagnosis" and "risk of breast cancer" were significantly elevated. The distribution of officer cases limits any analysis by MOS, and further analyses by MOS was limited to enlisted women.

Table 6. Standardized Incidence Ratio for Top 21 MOSs, Enlisted Army Women, 1980-1996

Military Occupational Specialty	Expected Cases	Observed Cases	SIR (95% CI)[a]	Rate[b]
Radio Operator-Maintainer	1.80	4	2.22 (0.60-5.69)	10.34
Information Systems Operator/Analyst	3.29	7	2.13 (0.85-4.38	22.00
Dental Specialist	2.70	5	1.85 (0.60-4.32)	18.11
Chemical Operations Specialist	2.59	4	1.55 (0.42-3.96)	21.74
Medical Specialist	5.03	7	1.39 (0.56-2.87)	10.99
Practical Nurse	8.26	11	1.33 (0.66-2.38)	35.80
Automated Logistical Specialist	18.89	22	1.16 (0.73-1.76)	13.98
Personnel Records Specialist	2.71	3	1.11 (0.22-3.24)	12.82
Administrative Specialist	23.08	25	1.08 (0.70-1.60)	17.42
Petroleum Supply Specialist	2.03	2	0.98 (0.11-3.55)	9.98
Motor Transport Operator	4.18	4	0.96 (0.20-2.45)	12.52
Finance Specialist	3.42	3	0.88 (0.10-2.56)	17.63
Medical Equipment Repairer	2.29	2	0.87 (0.10-3.16)	8.0
Medical Laboratory Specialist	2.41	2	0.83 (0.09-3.00)	16.11
Light Wheel Vehicle Mechanic	2.46	2	0.81 (0.09-2.94)	11.83
Record Telecommunications Operator	5.05	4	0.79 (0.21-2.03)	13.49
Military Police	3.86	2	0.52 (0.06-1.87)	10.31
Food Service Specialist	7.25	3	0.41 (0.08-1.21)	14.62
Personnel Administrative Specialist	3.87	1	0.26 (0.00-1.44)	15.74
Multi-channel Transmission Systems Operator-Maintainer	2.29	0	0.00 (-- -1.60)	11.29
Personnel Management Specialist	2.41	0	0.00 (-- -1.52)	14.20
Total	**109.85**	**113**	**1.03 (0.85-1.24)**	**14.83**

a - Standardized incidence ratio, 95% confidence interval
b - Per 100,000 person years, age-adjusted

Incidence Rate Ratios. Using the Poisson regression distribution procedure available in STATA (STATA Corporation, College Station, TX), incidence rate ratios (IRRs) were calculated for the enlisted cohort members. The cohort was stratified by

age, race, year of diagnosis, and organic chemical exposure using person-time as the weighting factor (Table 7). As expected, enlisted blacks had a significantly higher IRR than enlisted whites (1.43, $p = 0.04$). The IRR for all enlisted members increased with age (2.17, $p < 0.01$) and increased over the study period (1.24, $p < 0.01$).

Table 7. Cohort Analysis on Selected Organic Chemical Use, Year and Age at Diagnosis, and Race Using Poisson Regression, Enlisted Women, U.S. Army, 1980-1996

	Incidence Rate Ratio[a]	*p*	Confidence Interval (95%)
Solvent user[b]	1.48	0.03	1.03 - 2.12
Year of diagnosis[c]	1.24	<0.01	1.11 - 1.39
Age at diagnosis[d]	2.17	<0.01	1.98 - 2.39
Blacks[e]	1.43	0.04	1.01 - 2.07

a - Based on MOS at time of diagnosis
b - Moderate and high exposure potential rating compared to unexposed and low potential
c - 1989-1996 compared to 1980-1988
d - Age intervals 19-24, 25-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55+
e - Black women compared to white women

IRR for Organic Solvent Exposure Potential. Through analysis of industrial hygiene survey records, it was found that more than 150 of 300 enlisted MOSs were identified as having moderate or high exposure potential for organic chemicals. This included several MOSs described as administrative in the MOS job description. Thus, these MOSs would likely have been misclassified if their exposure assignment had been performed in the typical manner using job description alone, without the exposure potential ratings by the Army industrial hygienists. When the incidence rates for breast cancer among active duty women in jobs (MOSs) with moderate and high organic chemical exposure potential were compared to those with unexposed or low organic chemical exposure potential, as rated by Army industrial hygienists, the IRR was 1.48 ($p < 0.05$, CI 1.01-2.07).

DISCUSSION AND CONCLUSIONS

This study found a 48% increased risk of breast cancer among women holding jobs (MOSs) rated by Army industrial hygienists as having a moderate to high potential for exposure to at least one study organic solvent or chemical while on active duty between 1980-1996.

Previous studies have reported inconsistent results when attempting to identify occupations or classes of exposure based on occupations that were associated with increased breast cancer risk. The occupations with the most consistently reported elevated risks have been predominantly administrative in nature (10, 16, 17, 41, 42, 44, 46). Proposed causes for the increase primarily include delayed first full-term pregnancy or lack of exercise (44).

Several studies have used occupation as an estimation of exposure to solvents and other organic chemicals. Hansen (18) reported a significant increase in risk (OR

1.3, $p > 0.05$) for breast cancer among young women who worked in industries that used solvents, using a dichotomous variable for exposure without regard to levels of exposure or risk for exposure. Similar results were reported by Petralia and others (41) for Chinese women in China who had a high probability of exposure to moderate levels of benzene (SIR = 1.4, $p > 0.05$). Our findings are consistent with these studies (18, 41), indicating a possible increased risk for breast cancer in women who work in occupations that use organic solvents.

Several researchers have proposed that alcohol may act as a late-stage promoter of breast cancer. This is supported by recent studies demonstrating that alcohol consumption in the three to five years prior to diagnosis was a significant risk factor for breast cancer (6, 32, 55, 57). Organic solvents have also been proposed to be late stage breast cancer promoters (26). Numerous studies have concluded that the absence of workplace exposure measurements and assessments increase the misclassification of exposure and reduce the study power, making it difficult or impossible to evaluate the occupational breast cancer risk in these settings (16). In Chapter 2, we will overcome this limitation by using the Army industrial hygiene database to estimate exposure intensity for each MOS by task and year, improving the level of exposure classification from dichotomous categories to continuous measures.

This cohort analysis was limited to those women who were diagnosed with breast cancer while still on active duty. We do not, unfortunately, have information on the health status of women who served in the Army from 1980-1996 but who left before the end of follow-up. That is, the study design used here would not include a woman who was cancer-free when she left the Army during the study period and got breast cancer later. Thus, this study design is likely to produce risk estimates that are lower than the true risk.

This study reported an elevated number of cases diagnosed before age 35 years when compared to expected incidence in the general U.S. population for the same age groups (39). Moreover, approximately half of the cases occurred with less than 13 years since entry into the Army. Several factors may lead to these early cases. First, if organic solvents are late-stage promoters, then recent exposure should lead to more cases. Women in the Army after the age of 35 are usually assigned to supervisory positions and are less likely to have frequent exposure to organic solvents. Exceptions to this include those occupations that have solvent exposure regardless of pay grade or rank including nurses, histopathology technicians, and surgeons. The incidence rate of breast cancer for women 40 years of age and older decreased over the study period, while the mean age of women in the Army has been increasing. Second, more than one disease process may produce a diagnosis of invasive breast cancer. Because the diagnosis of breast cancer is based upon the tumor morphology, it is not possible to differentiate tumors with the same morphology but varying lag times. Spratt (24) reported the mean time for a breast cancer tumor to double in size was 260 days, with a range of ten to more than 7,000 days. He raised concerns that breast cancer may be three different diseases with the same cellular appearance. The first type is an aggressive tumor type that develops and spreads before it can be detected by the current technology, accounting for 13% to 17% of all breast cancer. The second type

(accounting for 68% to 77% of all breast cancer) has a five- to ten-year period from initiation to metastases, and the third type (accounting for 13% to 15%) grows but never spreads (24). Winchester (62) reported that women 35 years of age or younger appear to have a more aggressive form of breast cancer than those who develop cancer ten to 15 years later.

The purpose of this study was to conduct an evaluation of the risk of breast cancer and occupation, especially among women in jobs with a potential for exposure to solvents and other organic chemicals. The exposure assessment conducted to meet these study objectives used the linkage of multiple databases to perform occupational analysis and the use of exposure potential ratings by Army industrial hygienists to develop a qualitative measure of exposure (i.e., ever holding a job (MOS) rated as having a moderate to high potential for exposure to a study chemical). A qualitative exposure measure, rather than a more resource-intensive quantitative exposure assessment, was appropriate for this preliminary occupational analysis.

Given the present study finding, a more detailed, quantitative exposure assessment and epidemiologic analysis are warranted. The purpose of the quantitative exposure assessment would be to reduce the amount of exposure misclassification that can result from a qualitative exposure assessment and to provide quantitative exposure estimates that would permit the evaluation of an exposure-response relationship. The objective of the epidemiologic exposure-response analysis would be to determine whether exposure to any of the study chemicals in particular is associated with an increased risk of breast cancer and to quantify any exposure-response relationships. The U.S. Army population database used in this study offers several advantages for further quantitative analysis; it is a large study population with detailed occupational histories that can be linked to a set of air-monitoring data by year. The quantitative exposure assessment and exposure-response epidemiological analysis are reported in Chapters 2 and 3, respectively.

CHAPTER 2: AN ASSESSMENT OF ORGANIC CHEMICAL EXPOSURE FOR A CASE-CONTROL STUDY OF BREAST CANCER RISK AMONG WOMEN IN THE U.S. ARMY

INTRODUCTION

Women in the Army are employed in more than 1200 industrial, administrative, and professional occupations, many with recognized exposure to organic chemicals. In a review article, Lábreche and Goldberg(26) identified several organic chemicals (Table 8) suspected of increasing the risk of breast cancer, primarily by acting as late-stage promoters. As reported in Chapter 1, we conducted a cohort study of all women on active duty in the U.S. Army between 1980-1996 (N = 305,000) and found that women in certain occupations with a moderate to high potential for exposure to selected organic chemicals (as documented by Army industrial hygienists on at least one occasion) had a 48% greater risk for breast cancer than those who had no or a low exposure potential. This finding is consistent with the results of two civilian studies demonstrating an association between exposure to organic solvents and an increased risk for breast cancer (18, 41). However, these studies were limited in their ability to quantitatively assess the solvent exposures for those specific jobs. The objective of this work is to quantitatively assess the airborne chemical exposure concentrations and cumulative exposure to specific organic chemicals for a case-control study population drawn from a cohort of women on active duty in the U.S. Army.

Table 8. Study Organic Solvents and Chemicals for Exposure Assessment

<u>Chlorinated hydrocarbons</u>
Methylene chloride
Trichloroethylene
1,1,1-Trichloroethane
1,1-Dichloroethane
Perchloroethylene
<u>Aromatics</u>
Benzene
Gasoline and other blended aromatic solvents
Aviation fuels
Diesel fuel
Kerosene
Styrene
<u>Alcohols, aldehydes, and ketones</u>
Methyl ethyl ketone
Formaldehyde (with methanol)
Glutaraldehyde
Methanol
Ethanol
Isopropanol
<u>Blended solvents (aliphatic and aromatic)</u>
Paint solvents
Stoddard solvent
Petroleum distillates
Naphtha

BACKGROUND

In 1988, the Army instituted a centralized data collection system, the Health Hazard Information Management System (HHIMS), for industrial hygiene surveys (35). Data are collected and entered by the local industrial hygiene office and are uploaded to a central mainframe several times a year. The data are used at the local level to assist in medical surveillance decisions, identify and rank health hazards, track workplace monitoring sample submissions and results, set industrial hygiene survey priorities, and perform quantitative exposure assessments at the shop level. At the Army-wide level, the information is used to monitor health hazards across the Army, target resources for hazard abatement, and monitor compliance.

The Army uses an occupational classification system called the MOS that identifies groups of skills that are equivalent to job titles in private industry, as defined in the U.S. Census codes. The MOS for a particular job is standardized to provide a pool of trained workers capable of moving to a new location on short notice and providing a service, set of skills, and leadership required for the position. The work practices,

equipment, and chemicals used in these jobs are also standardized to ensure continuity between locations.

The Army adopted the use of job task as the fundamental unit for categorizing air sampling measurements and workplace evaluations in HHIMS. A task is defined as a collection of activities performed by a worker to accomplish a specific function. The HHIMS has more than 240 tasks from which the industrial hygienist must choose when evaluating a worker's exposure. The task identifiers may represent a simple action (e.g., painting with an aerosol can) to a more complex action (e.g., rebuilding an engine). For this study, the MOS will be used as the fundamental unit of analysis for the exposure assessment. This is the standard practice for retrospective exposure assessments, because MOS (job title) is the link between exposure and the individual members of the study population.

The MOS used in this study is a composite of all the tasks observed by industrial hygienists to be performed by an MOS across all locations in a particular year. The quantitative estimates of organic chemical exposure are averages weighted by task time. Air monitoring, other physical measurements, and industrial hygiene assessments based on observation are made for each of the tasks that comprise an MOS. Task sampling is performed primarily for identifying effective future interventions.

To assess the organic chemical exposures by MOS, more than 7,000 personal and general area task-based air samples of organic chemicals were obtained from the HHIMS database. Each air sample measurement was uniquely identified using a systematic series of codes that included the base location (similar to a ZIP code), the building number, room number, type of room, and the task monitored. Other information associated with each task-based air sample included the encrypted Social Security Number of the worker being monitored, chemical abstract number of the agent being monitored, sample collection time and date, the reported laboratory concentration, and the eight hour time-weighted average concentration calculated by the industrial hygienist.

In addition to air sampling results, the database included more than 34,000 workplace evaluations conducted by industrial hygienists that assessed the potential for exposure to the study chemicals. Exposure potential was rated because each workplace evaluation used the same unique location and task identifiers as the air-sampling database along with task-duration in hours per day, the evaluation date, and an inventory of stressors and roster of workers associated with each task. This paper presents the results of an exposure assessment of past exposures to organic chemicals that was developed using these quantitative and semi-quantitative measures of organic chemical exposure from the HHIMS database. Exposure intensity was calculated by year and MOS. The exposure intensity estimates by MOS and year were then linked with each study member's work history records. Cumulative exposure to specific organic chemicals and total organic chemicals and to individual organic chemicals and total organic chemicals were calculated for each member of the case-control study population.

Industrial Hygiene Sampling

Army industrial hygienists, like industrial hygienists in private industry, conduct air sampling for various reasons, but mainly for compliance, information gathering, and in response to worker complaints. Compliance sampling is sampling to determine if the operation or work site has a reasonable probability of exceeding some occupational exposure limit (OEL). Sampling data collected solely for compliance may under-represent work sites with air concentrations well below the OEL and over-represent work sites with air concentrations near or above the limit. Information gathering sampling is conducted when industrial hygienists need to obtain exposure data for a new or unfamiliar operation. The range and number of sample results depend upon the interest of the industrial hygienist. Sample results below the action level may lead the industrial hygienist to stop further sampling. Worker complaint sampling is usually conducted when workers are worried or think that they are being exposed to harmful chemicals. These samples may be of short duration, unrelated to task, and nonspecific in the expected outcome. In addition, air samples occasionally may be analyzed for chemicals that are not even used by the workers, because these chemicals may be a component of a mixture typically found in the operation being sampled (e.g., a sample may be analyzed for several solvents usually found in the carpet glues in a new building). These results are usually reported as "less than" concentrations, because an insufficient amount of the analyte was collected to quantify the actual concentration.

The Army industrial hygiene sampling strategy for a specific agent is based on several of the following factors: professional judgment, known health effects from exposure, the quantity of the agent in use, the frequency and duration of use, the conditions under which the agent is used, the effectiveness of engineering controls, and past monitoring data (34). During the walk-through phase of the industrial hygiene survey, the industrial hygienist assigns a Priority Action Code (PAC) for each agent and task. The PAC is based on the potential for an agent to exceed one-half of the OEL. The PAC assignments drive a predominantly compliance-based sampling strategy. The Army uses the lower of the OELs from the American Conference of Governmental Industrial Hygienists or the Occupational Safety and Health Administration. Frequently used chemicals with low OELs are sampled more than other chemicals. Once a sufficient number of samples have been collected to adequately assess the worker's risk, the number and frequency of samples for that agent decreases while exposure to other less toxic agents is assessed. Decisions for sampling priority are usually made at the installation level and are generally aimed at the highest risk chemicals for that location. The HHIMS database provided a distribution of airborne measurements for the agents of interest across all Army locations over ten years.

METHODS

Overview

Because the Army databases used in this study were created for purposes other than epidemiologic research, information from several databases had to be linked. To calculate cumulative exposure for each study subject, the MOS held by each study

member, the dates those MOSs were held, and the work locations of those MOSs had to be determined. No single database had all of the key elements required to place each worker in the locations in which they worked over their entire Army career. In the first stage of the exposure assessment, the set of MOSs held by the study subjects was matched to workplace air measurements collected between 1988-1996 to construct a job exposure matrix. The data sources and linkages are summarized in Figure 6. In the second stage, the work histories for each study member were linked to the job-exposure matrix and cumulative exposure was calculated for each subject.

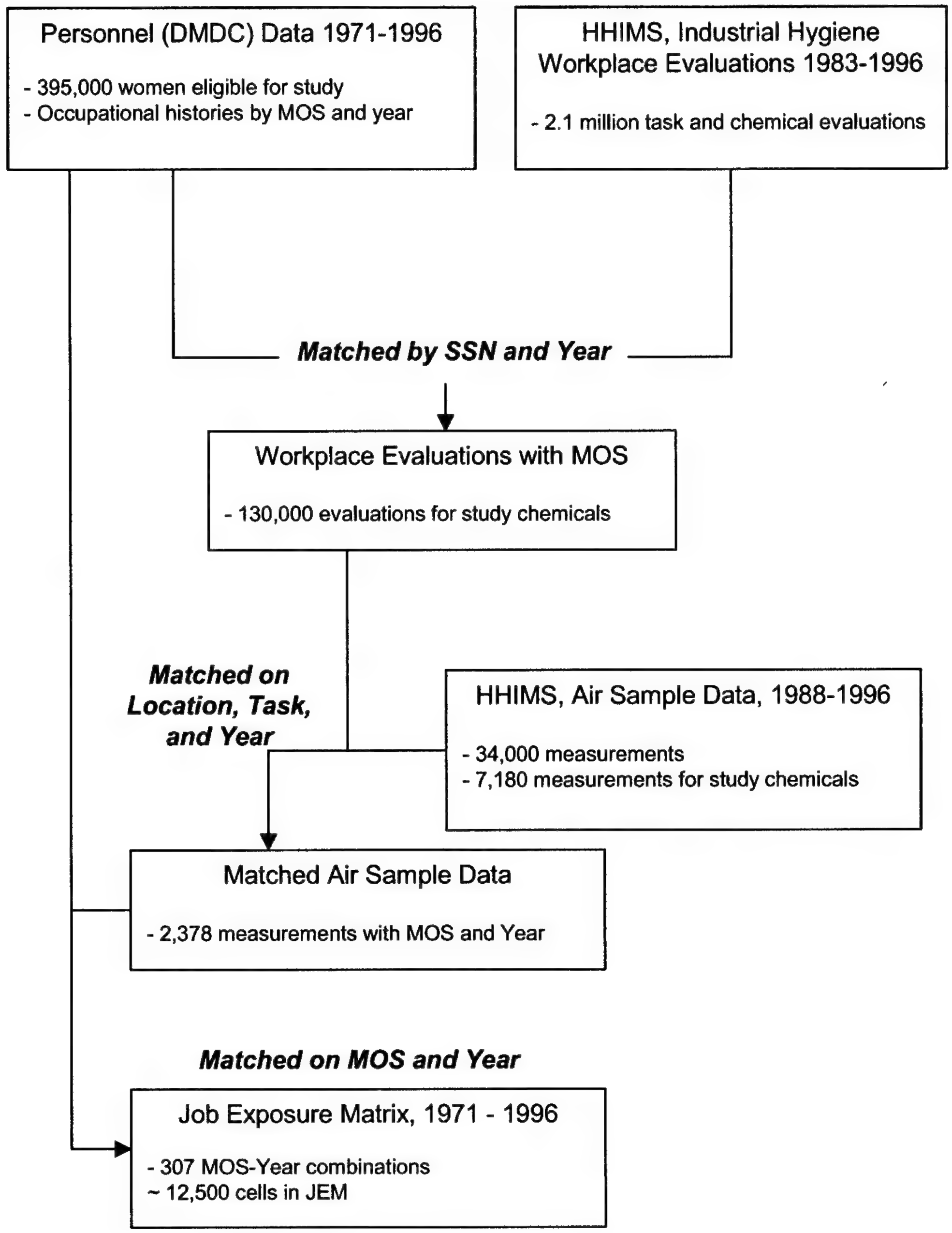
Definition of the Study Population

A case-control population was selected from a cohort of 305,000 women who served on active duty in the Army for at least one annual census between 1 January 1980 through 31 December 1996. The occupational histories for each study member during their employment in the Army were available from 1971 to the end of follow-up. There were 272 cases of invasive breast cancer identified from hospitalization and tumor registry databases among women on active duty in the Army. Because health, reproductive, and family histories provide important risk factor information, controls were selected from a subset of more than 25,000 cohort members who completed the HRA, administered by the Army at various times and places. The HRA is a voluntary, self-administered survey that collected information on age at menarche, number of primary relatives with a history of breast cancer, and history of alcohol and tobacco use. For each case, five controls were identified (N=1360) matched on risk age, to yield a total study population of 1632 women.

Occupational Histories

The occupational histories for the period of their active duty career in the Army were obtained for each of the 1632 women in the case-control study population from the personnel database within the TAIHOD (2, 3). The personnel database is a record of the jobs held by each Army member between 1971-1996 at the time of the annual Army census. The occupational information contained in the personnel database was initially limited to the primary MOS between 1971-1979 and expanded to include the duty MOS in 1980 (see below). Occupational histories were not available prior to 1971 because those records were not computerized.

Figure 6. Data Sources and Linkages to Construct the Job Exposure Matrix



Job Analysis

The level of analysis for the exposure assessment was the MOS, which is equivalent to a job title in civilian life. A detailed description of the process for assigning and documenting MOSs has been described in Chapter 1. Essentially, there are three types of MOSs: primary, secondary, and duty. The primary MOS is based upon the initial training and experience of the member at the time of enlistment or commission,

and it rarely changes. The secondary MOS is used to indicate any additional skills or qualifications that the member may acquire for job placement. The duty MOS is based upon the job title actually held by the worker and best reflects the tasks and duties assigned to the member. The duty MOS may be different than the primary and secondary MOSs. Primary MOS has been recorded in computerized personnel databases since 1971. Duty MOS is an optional field and did not appear in the database until 1975 and was inconsistently used until 1980.

Enlisted personnel are assigned a primary MOS at their entry into the Army and upon completion of initial job training. Officers may have two primary MOSs assigned. At least one MOS is used to classify the primary occupational skills within a branch or functional area. "Branch" is a grouping of officers that comprises an arm or service of the Army (e.g., Infantry, Aviation, and Intelligence), and "functional" area is an interrelated grouping of tasks or skills that require significant training and experience (e.g., Contracting and Research and Development). A second MOS may be used to describe additional skills or experience within a branch or functional area. For example, an Environmental Science Officer may be assigned a branch and functional area MOS of 67C for Preventive Medicine Services, and an area of concentration of 72D for Environmental Science. The TAIHOD may list either MOS in the primary MOS variable field for officers.

All job positions in the Army are coded using the MOS and additional codes for experience, special qualifications, and skills, permitting a match between the member and the position. MOSs are carefully standardized to be interchangeable across geographical locations, providing a consistent level of service and skills throughout the military. A duty MOS may be recorded when a member is assigned a job position other than their primary MOS. Because this study is focused on the actual job assignments, the duty MOS was used as the initial source of job. If a duty MOS was not recorded, the primary MOS was used. For those who entered service prior to 1971, the primary MOS listed in their earliest file was used in their occupational histories in the period between their entry into the Army and 1971.

Linkage of MOS with the Exposure Measures

Linkage of MOS with Workplace Evaluations. The HHIMS did not collect MOS information in the database during the study period, 1980-1996. The air monitoring results were not linked to specific MOSs, and the MOSs for individuals performing the monitored tasks were not recorded for more than 34,000 workplace evaluations. To link MOS information with the HHIMS, the MOS (from the personnel database of TAIHOD) was linked to the periodic workplace evaluations in HHIMS by SSN (encrypted to protect privacy) and by year. The results of periodic workplace evaluations, conducted by Army industrial hygienists, were recorded in the HHIMS by location codes, task, chemical, date, and the SSN of the assigned individuals. The location codes included the geographical location (e.g., base location), building number, room number, and the type of room (e.g., operating room), providing an exact location where the task performed by the worker was evaluated by the industrial hygienist. By linking MOS with the HHIMS by SSN and year, a profile of tasks and chemicals used

was created for each MOS. Table 9 provides an example of a task and chemical profile for a light truck mechanic compiled from more than 400 workplace evaluations.

Table 9. Task Profile for Light-Wheel Vehicle Mechanic (MOS 63B) for Study Chemicals

Task	Number of times sampled	Mean task duration (Hours/day)	Mean task weighted concentration (PPM) [a]
Engine rebuild	110	8.0	2.26
Maintenance	58	8.0	5.20
Aerosol can painting	18	0.7	0.01
Dip tank cleaning	6	1.2	0.04
Oil/lubricant handling and disposal	4	4.0	0.11
Manual wiping	4	1.5	0.04
Brush or roller painting	1	0.7	0.01

a - Parts per million

Linkage of MOS with Air Monitoring Data

From 1983-1996, more than 7,000 air samples for the study organic chemicals were reported throughout the Army. MOS was obtained by linking the SSN and year of the HHIMS data entry with SSN and year in the active duty Army personnel database from 1980-1996. More than 830 of 7,000 air-sampling measurements had an exact match on SSN and year, providing a direct MOS linkage with these measurements. The remaining air samples did not have a matching SSN entered, indicating that the result was for a general area or environmental sample, or that the worker was not an active duty Army members. To increase the number of samples for the exposure assessment, it was assumed that unsampled workers who performed the same task, in the same room, and used the same chemicals as the sampled workers would have similar exposure. Matching the MOS with the air monitoring data in the HHIMS database using this second set of criteria increased the number of organic chemical measurements associated with specific MOSs to 2,378.

Treatment of Air Monitoring Data

Development of the Task-Duration Scheme. As part of the industrial hygiene workplace evaluations, all tasks performed by an MOS across all locations were evaluated for average duration using hours per day. Ideally, all task-durations should add up to eight to 12 hours, depending upon the length of the shift, regardless of the number of people assigned to the shop. However, it was common to find MOSs where the task times summed to greater than eight to 12 hours. Further investigation into the Army industrial hygienist data recording found that because the evaluation was conducted at the workplace level, supervisors might have reported task-durations based upon the capabilities of the workplace instead of at the level of the individual, potentially overestimating the total duration of tasks performed by a particular MOS. For example, a vehicle repair shop with five workers with the same MOS may perform two distinct tasks: engine repair and body work. The supervisor may report the task-duration for

each as eight hours per day, instead of as a fraction of the total person-hours that the task required over an eight-hour day. The duration of tasks that are performed infrequently may not be precisely assessed due to the reporting requirement that the duration of every task be recorded in hours per day. For example, some of the maintenance work performed in the Army is preventive in nature and scheduled during regular and infrequent intervals, (e.g. monthly or quarterly). The assignment of a daily duration to these tasks is likely to be imprecise between workplaces and industrial hygienists.

For the purpose of evaluating exposure, an MOS was considered to be the average of all the tasks that industrial hygienists observed being performed to fulfill the duties of that MOS as it was performed across all work locations in a given year. It is a composite representing the average MOS in a particular year and does not necessarily represent the actual tasks performed by a given individual or the MOS as performed on a particular day in a particular location. To obtain an estimate of the durations of tasks that comprised each MOS across the Army, a task-duration fraction was calculated using the number of hours for each task that was performed, divided by the number of hours per day for that particular work location—usually eight hours (Equation 1).

$$\text{Task-duration fraction} = \text{Task-duration (hours per day)/ 8 hours} \tag{1}$$

Calculation of the Task-Duration Weighted Average Concentration of Organic Chemicals by MOS. Although all air-sampling measurements were reported in the HHIMS as eight-hour time weighted averages (TWA), not all samples represented a particular worker's average daily exposure to particular organic chemicals. Some samples were taken in response to worker complaints or for infrequently performed maintenance actions. In addition, it was standard Army practice to report measurements below the limit of detection as less than the eight-hour time-weighted average. When a measurement was reported as "less than" the limit of detection and greater than 10% percent of the current OEL, the reported average concentration was changed to 10% percent of the current OEL. If the less than detected measurement was less than 10% percent of the OEL, it was left unchanged. Thus, to give more weight to tasks that were performed most frequently and to minimize the effect of infrequent tasks on the estimate of average exposure, a task-duration weighted estimate of exposure was calculated by multiplying the time-weighted average by the task-duration fraction (Equation 2).

$$\text{Task-duration weighted average} = \text{Measured TWA} \times \text{Task-duration fraction} \tag{2}$$

The total organic chemical fraction was calculated by dividing the task-duration weighted average (TDWA) by the current OEL for each chemical by MOS and year.

$$\text{Total organic chemical fraction} = \left(\frac{TDWA_1}{OEL_1} + \frac{TDWA_2}{OEL_2} + \frac{TDWA_3}{OEL_3} + \ldots \frac{TDWA_n}{OEL_n}\right) \tag{3}$$

Annual mean task-duration averages were calculated for each MOS and chemical and for total organic chemical fractions for each year that samples were reported in the HHIMS.

Estimation of the Concentration of Organic Chemicals by MOS and Year for the Job Exposure Matrix

Job Exposure Matrix. The calculated annual task-duration weighted averages were used to construct regression models to estimate the average concentration of organic chemicals for a job exposure matrix (JEM), as shown in Equation 4.

$$\text{Task-duration weighted average} = \text{intercept} + \beta * \text{Year} \qquad (4)$$

The JEM was constructed for each organic chemical, giving the concentration of the chemical by MOS for each year of the study. The task-duration weighted average for each MOS and chemical was tested for significant trends using the following criteria to assign the organic chemical concentrations to the JEM using the regression models:

a. If the linear regression results for a particular model were significant and the model was constructed with at least six task-duration weighted average concentration measurements in at least four years (56), the regression equation was used to estimate the annual concentration for each year of the study, including the study years 1980-1983, when air monitoring data were not available in the HHIMS database. If the regression equation estimated a value less than the measured weighted mean, the actual task-duration weighted mean concentration for that year was substituted to avoid underestimating the annual exposure for that particular year. The time period of four years was used to prevent extreme measures that changed over just a few years from estimating extremely low or high concentrations for the earlier, unmeasured years. For example, if a chemical had a few samples in 1992 that were five times greater than the mean in 1996, the regression analysis created a slope so steep that, when it was extrapolated backward to the beginning of the study period, it yielded an unreasonably high estimate.

b. If the results of the model were not significant, or if a model was constructed with less than six measurements per year over at least four years, then the overall arithmetic mean concentration of an organic chemical was used.

Estimation of Cumulative Exposure. Worker cumulative exposures for individual chemicals and total organic chemicals were obtained by merging the occupational histories and the job exposure matrix using PROC SQL in SAS version 6.04, (SAS Institute, Cary, NC). For each study subject, the chemical concentrations and total organic chemical fractions experienced each year of every MOS held during her Army service were summed:

Cumulative exposure (ppm-year) =
$\sum$MOS concentration estimate (ppm) * Duration of MOS (years) (5)

Cumulative total organic fraction (years) =
$\sum$MOS total organic chemical fraction * Duration of MOS (years) (6)

RESULTS

Mean Task-Duration Weighted Concentrations

Table 10 summarizes the 2,378 workplace organic chemical air measurements used in this study. The measurements were weighted based on the task-duration fraction described earlier. Of the 23 chemicals proposed for the study, 18 had individual-level air measurements in the database. The remaining five chemicals did not have a match between the Army active duty personnel database and the air-sampling database. The workplaces using these chemicals may have employed only civilian workers or Army Reserve personnel.

Table 10. Mean Task-Duration Weighted Concentrations for Study Chemicals

Chemical	N	Mean TWA (PPM)[a]	SD[b]	Range (PPM)	Above Action Level[c]
Formaldehyde	447	0.06	0.15	<0.00 - 1.85	20.4
Xylene	403	1.07	1.89	<0.001 – 25.00	0.8
Toluene	389	0.97	1.46	<0.001 – 12.83	0.6
Stoddard solvent	323	6.18	11.7	0.002-137.28	1.3
Methyl methacrylate	149	3.80	8.08	0.004-106.00	2.9
Methylene chloride	129	1.72	7.23	<0.001 – 61.50	3.3
Naphtha	108	2.16	10.83	0.004-106.00	0
Ethyl alcohol	66	4.95	8.08	0.221 – 37.50	2.2
Benzene	64	0.41	0.84	0.002 - 6.53	5.8
Methyl alcohol	48	0.84	1.41	0.119 - 7.71	0
Methyl chloroform	59	0.78	1.66	<0.001 – 11.95	0
Methyl ethyl ketone	39	2.27	2.55	<0.001 – 10.26	0
Diesel fuel	28	1.83	3.2	0.262 – 14.91	12.0
Trichloroethylene	26	2.44	1.58	0.142 - 5.00	3.9
Styrene monomer	22	2.19	1.80	0.013 - 5.00	0
Isopropyl alcohol	19	3.12	2.99	0.146 – 10.00	0
Petroleum distillates	17	1.67	1.2	0.466 - 3.84	0
Perchloroethylene	17	0.88	1.0	0.046 - 2.60	0

a - Parts per million
b - Standard deviation
c - Percentage based on occupational exposure limit at the time of the unweighted measurement

The weighted airborne concentrations were well below the current OEL for all chemicals. This was expected for several reasons. First, it is Army policy to use measurements in excess of the action level instead of the OEL for implementing

controls, increasing efforts to keep workplace levels low (13). Action level in the Army is defined as one-half the OEL unless otherwise identified in a specific standard (e.g., OSHA) (34). Second, Army activities are required to implement control measures unless such installations are technologically unfeasible (13). In addition, many work practices used by the Army are standardized through occupational guidelines and training. Practices that may lead to higher exposures can be altered or eliminated in favor of those that reduce potentially hazardous airborne concentrations for all workers within that specific MOS. With the exception of formaldehyde, few unweighted workplace measurements exceeded the action level, and the overall percentage over the action level was 5.4, as reported in the HHIMS by the industrial hygienist who took the sample.

Table 11 shows the annual mean concentration for the five most frequently measured chemicals in the study. Toluene, formaldehyde, and Stoddard solvent had linear regression models with significant negative slopes over time ($p < 0.05$). These chemicals had trends that indicated that workplace measurements decreased over time, but the highest estimated concentrations were still below the current OEL. This is expected because the actual measurements used in the linear regression model were well below the OEL and workplace conditions improved, including an increased use of engineering controls over the same time period. The lack of trend in the arithmetic mean for each of the remainder of the chemicals may be explained by the same problems found in most exposure analysis studies (52). A lack of trend in these chemicals was due to the high variability of the measurements between the years. This was probably due to a combination of the local control of sampling priorities and differences in working conditions and engineering controls (15).

Mean Task-Weighted Concentrations by MOS

Formaldehyde. Formaldehyde is primarily used in the Army in medical, dental, and embalming procedures, but is also found in water-repellant treatments for clothing, paper treatments, and as a minor ingredient in many industrial products. Medical uses and embalming account for 86% of all formaldehyde samples in the matched air-sample database. In Table 12, the mean task-weighted concentration for formaldehyde is compared for several MOSs. Pathologists and Graves Registration Specialists, civilian equivalent to embalmers, had the highest mean concentration at 0.07 ppm. The geometric standard deviations (GSD) for jobs where formaldehyde was frequently used were all below two, indicating a small amount of variability within MOS. Holness and Nethercott reported formaldehyde concentrations ranging from 0.08 ppm to 0.81 ppm, with a mean concentration of 0.21 ppm in embalming rooms with general dilution ventilation and 0.55 ppm in embalming rooms with the ventilation turned off (20). The range of weighted formaldehyde concentrations during embalming in this study was 0.01 ppm to 0.47 ppm with a GSD of 1.66.

Table 11. Mean Task-Weighted Concentrations for Selected Solvents by Year Sampled

Chemical	1988	1989	1990	1991	1992	1993	1994	1995	1996
Formaldehyde		0.34 (11)[a]	0.06 (21)	0.02 (24)	0.02 (53)	0.07 (42)	0.06 (62)	0.02 (52)	0.04 (46)
Xylene	0.16 (8)	2.34 (16)	2.06 (17)	1.51 (94)	0.73 (122)	1.14 (43)	0.33 (17)	0.64 (23)	1.12 (30)
Toluene	0.27 (6)	3.63 (4)	2.54 (13)	1.33 (106)	0.83 (109)	1.02 (47)	0.40 (29)	0.36 (26)	0.06 (32)
Stoddard solvent	0.58 (1)	0.75 (2)	5.28 (6)	7.40 (82)	11.22 (68)	11.52 (37)	1.65 (54)	0.96 (29)	1.30 (35)
Methyl methacrylate	0.38 (5)	1.46 (4)	10.62 (11)	7.05 (13)	4.57 (38)	2.72 (17)	2.79 (25)	2.86 (21)	0.33 (2)

a - Mean (number of samples)

Table 12. Mean Task-Weighted Concentrations for Selected Job Titles and Study Chemicals

MOS [a]	Chemical	Mean (N) [b]	SD [c]	GSD [d]
Light wheel vehicle mechanic	Xylene	0.69 (60)	0.93	1.99
	Stoddard solvent	7.04 (66)	12.24	1.99
Wheel vehicle repairer	Stoddard solvent	15.03 (18)	34.28	3.60
Heavy wheel vehicle mechanic	Stoddard solvent	6.09 (19)	10.32	3.32
Medical specialist	Xylene	0.76 (31)	1.37	1.52
	Formaldehyde	0.04 (73)	0.10	1.76
Medical laboratory specialist	Xylene	1.05 (52)	3.53	1.42
	Formaldehyde	0.07 (60)	0.13	1.37
	Ethyl alcohol	3.03 (18)	3.04	0.63
Pathologist	Formaldehyde	0.12 (88)	0.28	1.59
Graves registration specialist	Formaldehyde	0.07 (56)	0.09	1.66
General surgeon	Ethyl alcohol	4.33 (23)	10.49	1.26
Dental specialist	Methyl methacrylate	4.39 (144)	8.77	1.51
Prosthodontist	Methyl methacrylate	0.29 (4)	0.30	1.15

a - Military Occupational Specialty
b - Mean in parts per million and the number of measurements
c - Standard deviation
d - Geometric standard deviation

Histopathology labs are another source of daily exposure to formaldehyde. Formaldehyde is used to preserve anatomical specimens for gross and microscopic examination. The Army has two MOSs that are typically assigned to the histopathology labs: pathologists (officer) and medical laboratory specialists (enlisted). The mean task-duration weighted concentration for pathologists was 0.12 ppm with a GSD of 1.59, and for medical laboratory specialists (laboratory technicians), 0.07 ppm with a GSD of 1.37. The formaldehyde levels in histopathology labs ranged from <0.001 to 1.8 ppm. These compare favorably to those found in a study of ten histopathology laboratories, having formaldehyde levels in the gross examination area that ranged from 0.2 to 1.9 ppm (23). The difference in exposure levels between pathologists and laboratory specialists may be due to the amount of gross examinations performed by pathologists as their primary exposure to formaldehyde, while medical laboratory specialists prepare and read slides and perform other chemical analysis that do not involve formaldehyde exposure. Medical specialists (e.g., emergency medical technicians) provide support to all areas within a hospital and thus may handle formaldehyde infrequently and for short periods of time, typically less than five minutes per use; hence, the lower mean-weighted concentration (0.04 ppm) and higher GSD (1.76).

Xylene. Xylene is primarily used in the Army as a solvent in paints and cleaning compounds in industrial areas and in processing slides in pathology laboratories. More than 45% of all xylene samples were taken in maintenance areas such as auto garages and equipment repair shops, and 30% were taken in medical areas. Medical laboratory specialists had the highest xylene weighted measurements: 1.05 ppm and a GSD of 1.42. The mean xylene concentrations for Light Wheel Vehicle Mechanic was 0.69 ppm (range of <0.01 to 5.5 ppm) and Medical Specialist was 0.76 ppm. In the civilian study of ten histopathology labs, xylene measurements ranged from 2 to 102 ppm (23). In this study, the weighted xylene concentrations ranged from <0.01 ppm to 25 ppm in Army histopathology labs. The differences between the Army and Kilburn study results were probably due to improving engineering controls over several years between 1988 and 1996 in Army hospitals. (The samples used in the Kilburn study were taken before 1985.) Because the xylene levels are well below the action level, the lower concentrations may be an indirect benefit of the engineering controls installed to control formaldehyde in the histopathology lab. The Permissible Exposure Limit for formaldehyde changed in 1988 from 3 ppm to 0.75 ppm.

Methyl Methacrylate. Methyl methacrylate (MMA) is a monomer used in acrylic plastics, primarily in dental prosthetics. The MMA monomer, a highly volatile liquid, is mixed with powdered MMA to form the plastic. Enlisted dental specialists had a mean task-duration weighted concentration of 4.39 ppm with a GSD of 1.51, and prosthodonists were exposed to a mean task-duration weighted concentration of 4.33 ppm with a GSD of 1.15. Again, these measurements represent daily routines performed under specific conditions not likely to produce much variability. In a study of two dental laboratories in Canada, MMA measurements ranged from 0.12 to 2.7 ppm with a GSD range of 2.9-3.3 (40).

Stoddard Solvent. Stoddard solvent is a general use petroleum distillate used throughout the Army, including medical areas. The most frequently evaluated users of Stoddard solvent work in the auto trades (e.g., vehicle mechanics and repairers). Because Stoddard solvent is used under a wide variety of conditions, including parts cleaning, spraying, dipping, and wiping, the GSDs were the highest observed of the most frequently measured chemicals. While the results reported are for eight-hour work shifts, typical worker exposure to the solvent would be intermittent throughout the day. The range of Stoddard solvent measurements in auto repair trades was 0.02 to 137 ppm, and the mean task-duration weighted concentrations were two to four times greater than those observed in medical MOSs.

Estimation of the Concentrations of Organic Chemicals by MOS and Year for the Job Exposure Matrix

Of the 23 chemicals listed in Table 8, there were insufficient air monitoring data to include glutaraldehyde, gasoline, kerosene, aviation fuels, and 1,1,1 trichloroethane in the job exposure matrix. The JEM exposure intensity estimates for the 18 chemicals with sufficient data were assigned according to the criteria described previously in the Methods section. Exposure intensity estimates meeting criteria for assignment using regression equations: Light Wheel Vehicle mechanic (toluene and Stoddard solvent), Medical Laboratory Specialist (formaldehyde), and Pathologist (formaldehyde). Each had significant negative slopes. Where the regression line predicted annual concentrations less than the limit of detection for formaldehyde, the limit of detection was substituted. The estimated values were all less than the OEL for that year. All other assignments used the overall arithmetic mean concentration of each organic chemical for each MOS-year combination.

Estimated Cumulative Exposure

Table 13 demonstrates how cumulative exposure was calculated for each study member. The woman used for this example entered the Army in 1989 as a medical equipment repairer, changed jobs in 1992 to medical specialist, and was a practical nurse from 1994 to the end of follow-up in 1996.

Table 13. Example Cumulative Exposure Profile and Work History for Xylene

MOS [a]	Year	Mean TDWA (PPM*Year) [b]
Medical equipment specialist	1989	1.85
Medical equipment specialist	1990	1.85
Medical equipment specialist	1991	1.85
Medical specialist	1992	0.76
Medical specialist	1993	0.76
Practical nurse	1994	0.73
Practical nurse	1995	0.73
Practical nurse	1996	0.73
Totals	**8 years**	**9.26 ppm*years**

a - Military Occupational Specialty
b - Task-duration weighted average in parts per million*years

The distributions of cumulative exposure for the five most frequently measured organic chemicals are given in Figures 7–11. The population for which these cumulative exposure estimates have been calculated is from a case-control study of breast cancer among U.S. Army women using the organic chemicals with the five highest number of air samples in the HHIMS database: formaldehyde, xylene, toluene, Stoddard solvent, and methyl methacrylate. Due in part to the annual mean task-duration weighted concentrations, the range for the estimated cumulative exposures was narrow. The cut-points for the exposure categories were selected as functions of the current OEL, usually 50%, 25%, or 10% of the OEL.

Figure 7. Cumulative Formaldehyde Exposure in a Case-Control Study Population

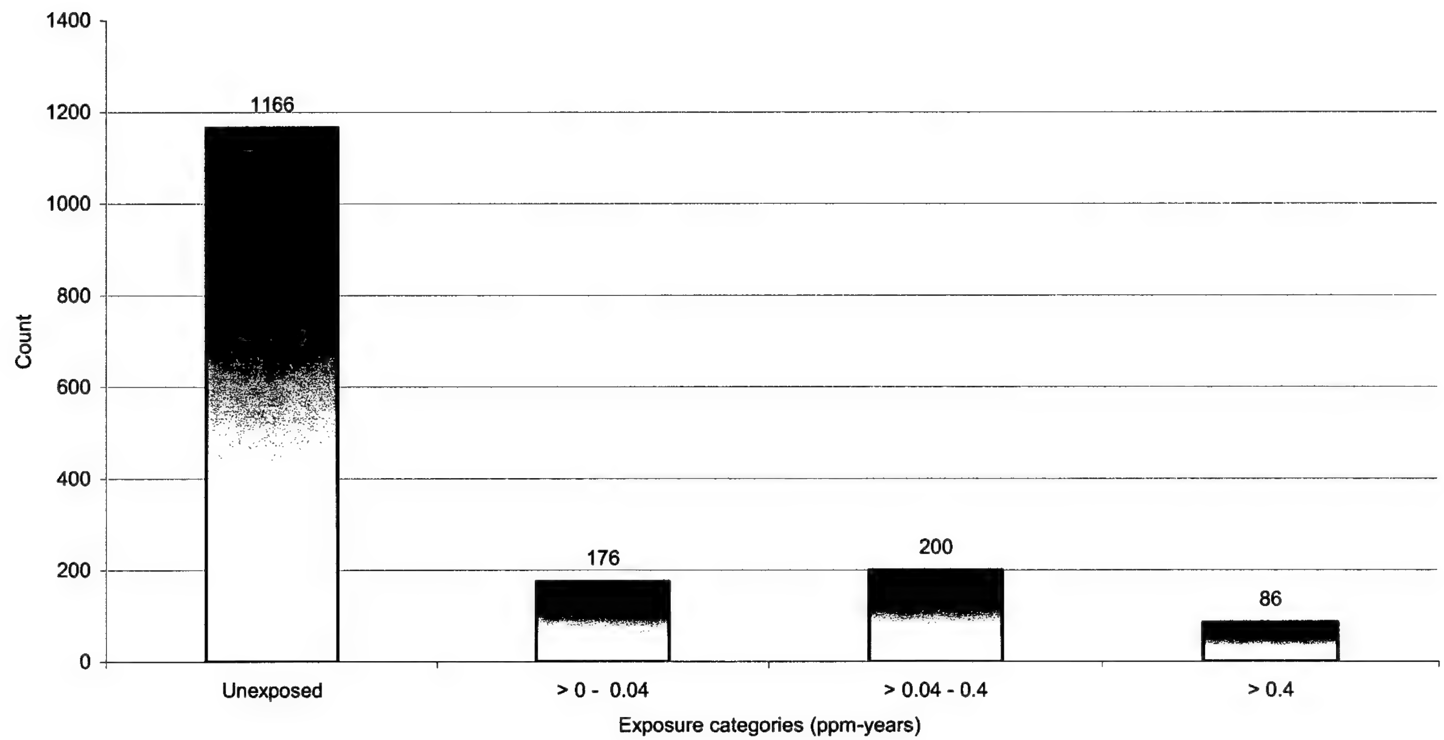


Figure 8. Cumulative Xylene Exposure in a Case-Control Study Population

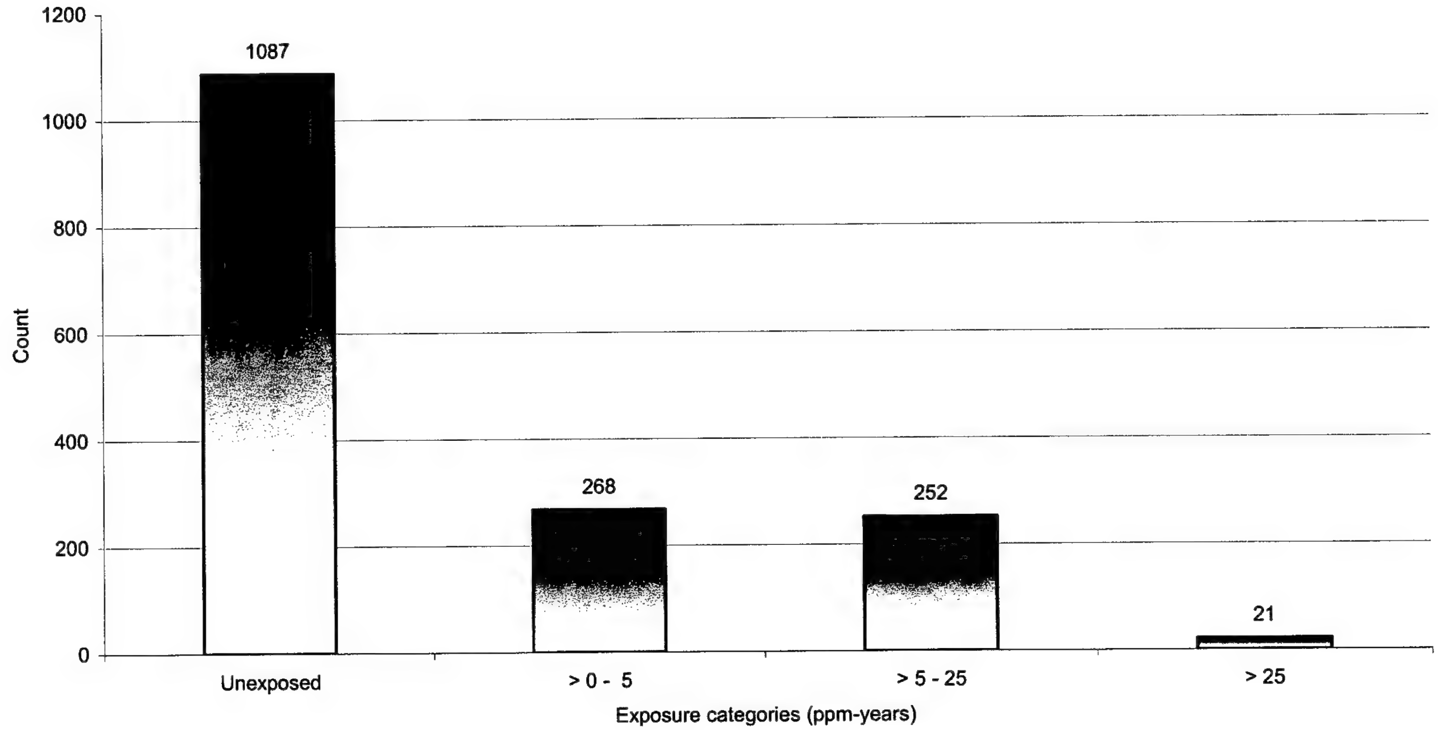


Figure 9. Cumulative Toluene Exposure in a Case-Control Study Population

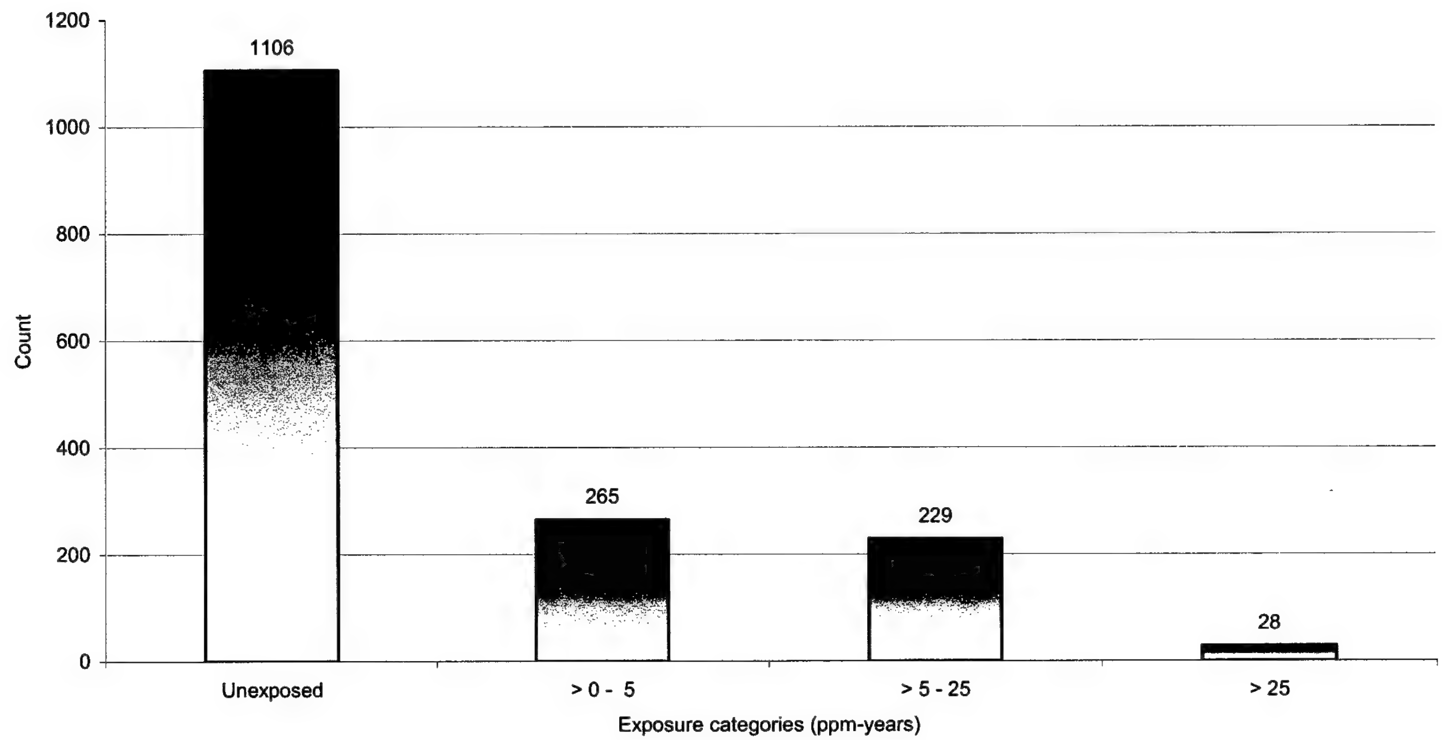


Figure 10. Cumulative Stoddard Solvent Exposure in a Case-Control Study Population

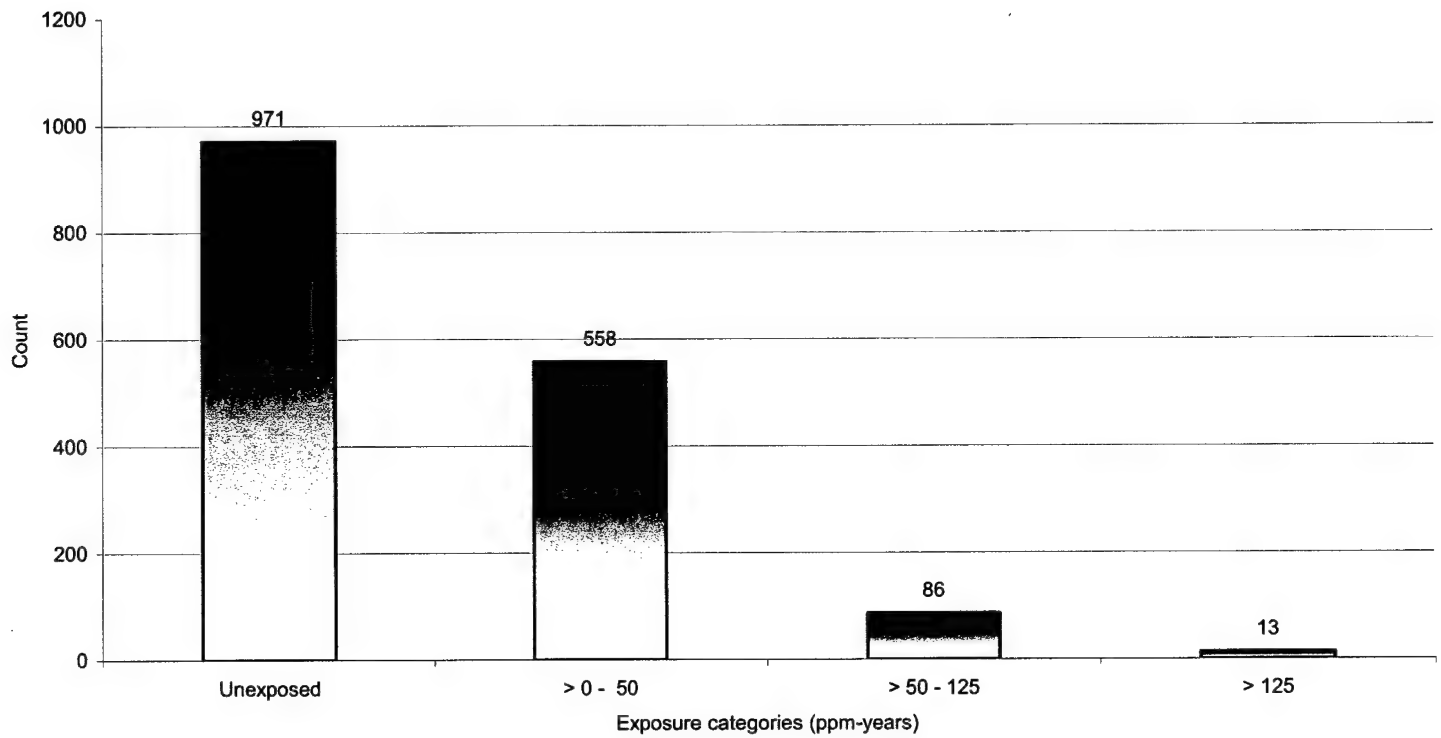
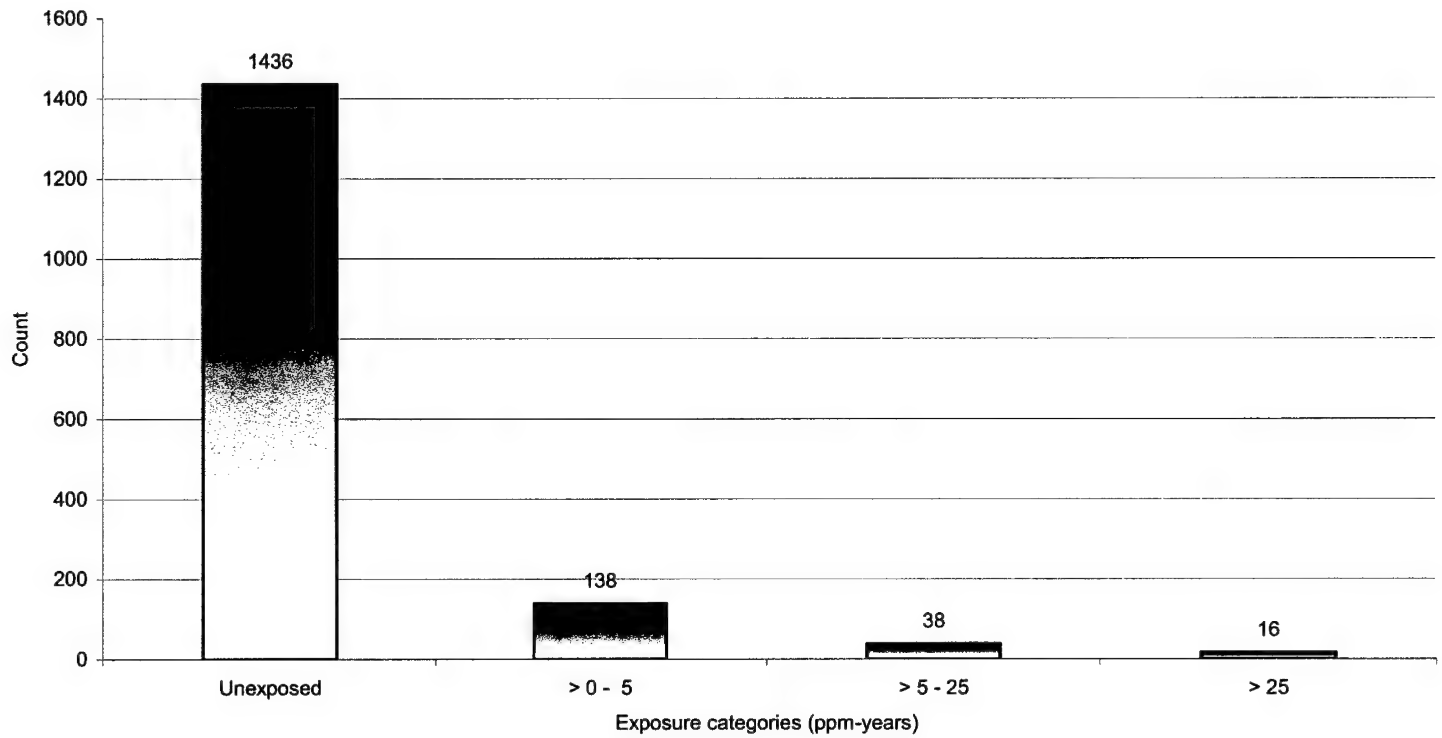
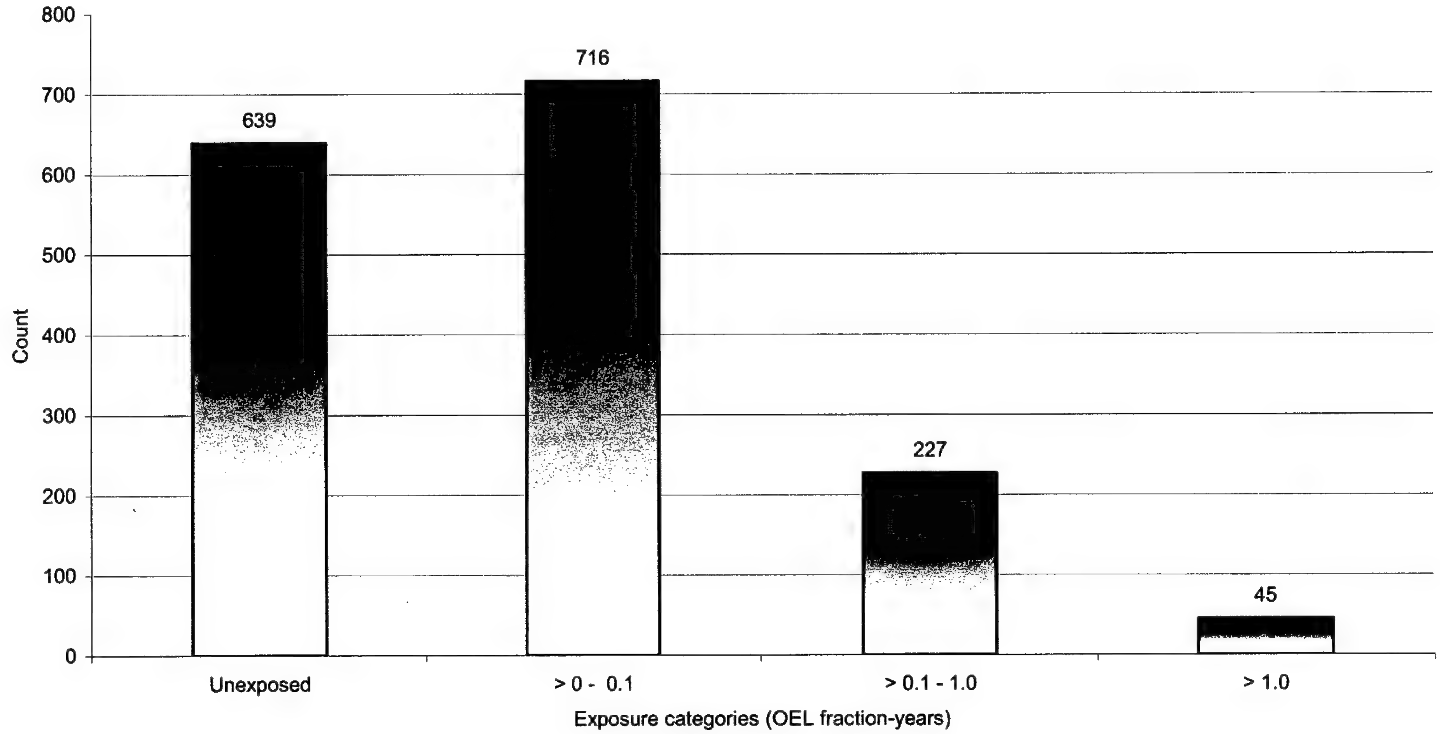


Figure 11. Cumulative Methyl Methacrylate Exposure in a Case-Control Study Population



To assess worker cumulative exposure to all of the chemicals in the study, the mean task-duration weighted concentrations are expressed as a fraction of the current OEL and the fractions summed to obtain individual estimates of cumulative organic chemicals. As expected, 989 of 1628 subjects (61%) had exposure to at least one study chemical, and 300 individuals had more than 50 MOS-chemical-year combinations in their estimation of cumulative exposure. This indicates that women in the Army are employed in jobs with exposure to multiple chemicals during their career. The cut-points for cumulative exposure to the study chemicals were one and five OEL fraction*years (Figure 12).

Figure 12. Cumulative Exposure to the Study Chemicals as Total Organics for a Case-Control Population



DISCUSSION AND CONCLUSIONS

Estimation of Exposure

Based on the available comparisons for selected occupations in the literature, the estimates of exposure based on actual measurements used in this study compare favorably to those previously published for similar jobs and industries in the civilian sector. The limitations of this exposure assessment are primarily related to the industrial hygiene sampling strategy and the short-term task rather than jobs for which measurements were available. In addition, chemicals that were expected to be below the action level had a lower priority and were less likely to be sampled. Operations that did not interest individual industrial hygienists, regardless of the expected workplace concentration, were less likely to be sampled. And, finally, workplaces where workers did not complain about possible exposure to chemicals were less likely to be sampled. As reported in Chapter 1, Army industrial hygienists documented more than 300 MOSs out of all the MOSs employing Army women, with moderate to high potential for exceeding the action level for the study chemicals. The population used for this study had 300 MOSs total, with 150 of those MOSs rated as having a moderate to high exposure potential, but with only 80 MOSs with air-sampling measurements. Only formaldehyde had actual measurements near or above the action level. Several studies have concluded that subjective judgments by industrial hygienists have a high degree of variability when attempting to estimate categories of exposure (45, 51).

The method of estimating annual mean concentrations for unsampled years in the JEM also had limitations. Women began to work in the industrial areas in the Army shortly after 1972. The air measurements used in this study's exposure estimation were based on samples from Army men and women because, conceptually, they were doing the same job. If the samples were predominately from men, and men had higher exposures than women, the JEM would overestimate the true annual exposure for the study population. This was not expected in MOSs traditionally associated with women, such as health care and administration, but might be the case for jobs that were not traditionally held by women prior to 1988. This is because when women first entered these jobs, they may still have been given a lighter duty than men, until later years when they were more fully integrated into these positions.

Changes in the workplace environment would also affect the accuracy of the estimates. The method of using the annual mean or predicted concentrations by year from the linear regression models does not take into account changes in exposure regulations, installation of engineering controls, and substitution of materials. While it is probable that workers were exposed to levels that exceeded an OEL, it is unlikely that the exposure went undetected and unabated for several years. The Army historical industrial hygiene records were not used to validate the estimates because they were not computerized nor easily accessible. The results of this study will be used to target specific chemicals for future validation efforts of the exposure assessment model.

The greatest value from the exposure assessment model was from the use of task-duration to weight the actual measurements. The task-duration fraction provided a method for assigning each measurement a relative value for a particular MOS. The histograms (Figures 7-11) show that most Army personnel are either unexposed or in the lowest exposure category for any specific chemical or the total organic chemical fraction (Figure 12), a reasonable finding when the Army is viewed as a major corporation with a large component of its work force performing administration.

The JEM created for this study was used to estimate measures of cumulative exposure for a case-control study population for breast cancer in the Army. The structure of the JEM permitted the use of time windows for the calculation of cumulative exposure to explore the effects of exposure at various times in a women's chronological and reproductive life for the risk of breast cancer. The results of this analysis are presented in Chapter 3. The programming used to merge the databases that populate the JEM can be used for estimating annual concentrations for any chemical or class of chemicals for epidemiologic studies of U.S. Army populations.

CHAPTER 3: A CASE-CONTROL STUDY OF EXPOSURE TO ORGANIC CHEMICALS AND THE RISK OF BREAST CANCER AMONG WOMEN IN THE U.S. ARMY

INTRODUCTION

Recent studies reported that women employed in jobs or industries with occupational exposure to organic solvents had a significantly increased risk for breast cancer (18, 41). Several studies have identified a number of organic chemicals as potential breast tissue carcinogens and proposed possible mechanisms for their carcinogenic activity (16, 17, 57). These organic chemicals are summarized in Table 14. In the cohort analysis described in Chapter 1, a 48% increase in breast cancer incidence was found among enlisted women on active duty whose job at diagnosis had a moderate to high potential for exposure to the organic chemicals listed in Table 14, hereafter referred to as the study chemicals, when compared to unexposed and low organic chemical exposed occupations. Based on the findings of the cohort analysis, it was decided that a quantitative exposure assessment was warranted. The results of the exposure assessment are reported in Chapter 2. The results of the exposure-response study using the detailed exposure assessment are reported here.

Table 14. Study Organic Solvents and Chemicals for Case-Control Study

1,1,1-Trichloroethane
1,1-Dichloroethane
Benzene
Diesel motor fuel
Ethanol
Formaldehyde (with methanol)
Gasoline
Isopropanol
Kerosene
Methanol
Methyl ethyl ketone
Methyl methacrylate
Methylene chloride
Naphtha
Paint solvents
Petroleum distillates
Perchloroethylene
Trichloroethylene
Stoddard solvent
Styrene

It was also observed from the cohort analysis that a majority of the cases occurred among premenopausal women. It was thus hypothesized that the timing of the organic chemical exposure with respect to breast tissue development might be

related to the observed increase in breast cancer risk. To investigate the timing of exposure, a biological model was constructed based on a review of the literature concerning breast tissue development over a woman's lifetime. The model was used to identify biologically significant time windows to assess the effects of exposure to the study organic chemicals.

The objectives of this study were to investigate the risk of breast cancer among women occupationally exposed to selected organic chemicals and solvents, and to evaluate the role of exposure timing in each woman's reproductive life and the occurrence of breast cancer.

BACKGROUND

Breast Tissue Development

In Chapter 1, a detailed model was presented of the physiologic changes and time course of breast tissue development, based on a review of the literature (Figure 1). In this chapter, the model was used to create exposure variables corresponding to time windows related to development of breast tissue. Briefly, the stages of breast tissue development correspond to the reproductive milestones for women including their own birth, menarche, first full-term pregnancy, and menopause. Each milestone can be characterized by the evolution of lobules in the breast (25, 48-50).

All women are born with and begin breast development with Type 1 lobules. As a woman approaches puberty, Type 1 lobules mature to Type 2, which are responsible for developing the ductal system. During pregnancy, the Type 2 lobules are stimulated to evolve to Type 3 and, if the pregnancy is full-term and the woman breastfeeds, Type 3 lobules become Type 4 lobules. Research has shown that women with the highest proportion of Type 3 and 4 lobules have a lower risk of breast cancer because these lobules are refractory to cancer (49). The breast tissue of nulliparous women is dominated by Type 1 and 2 lobules and is more susceptible to agents with carcinogenic effects. Because breast tissue development slows after age 25 years, the protective effect of first pregnancy diminishes for a woman after she reaches the age of 20 years and becomes an increasing risk factor for breast cancer the longer she delays the birth of her first child. Women who had their first pregnancy before age 30 years and developed breast cancer were found to have the same proportion of Type 1 and 2 lobules as nulliparous women (49).

Incidence of Breast Cancer Among U.S. Army Women

A preliminary cohort analysis of the incidence of breast cancer among enlisted U.S. Army women was conducted using the occupation at the time of diagnosis. Enlisted women were selected because they comprised 90% of the U.S. Army female population and because their occupations included industrial and medical jobs with the greatest potential for occupational exposure to the study chemicals (Table 14). The study chemicals were selected based on recommendations found in several papers that reported or suspected an association with breast cancer. The women's occupation at

the time of diagnosis was used because more than 80% of enlisted women had the same job throughout their Army careers. As described in Chapter 1, we found a 48% statistically significant ($p = 0.05$) increase in the relative risk of breast cancer among enlisted women having occupations judged by Army industrial hygienists to have a moderate to high potential for exposure to the study organic chemicals when compared to those having occupations with no or low potential for exposure. The results of the cohort analysis indicated that a more detailed assessment of exposure was warranted and a quantitative exposure assessment was conducted.

Breast Tissue Development and Timing of Exposure

The association between breast cancer and exposure to ionizing radiation depends upon the level of exposure and the degree of breast tissue development at the time of exposure (28). The longer the first pregnancy is delayed, the longer the more susceptible breast lobules, Type 2, are available for carcinogenic action, and the wider the time window for potentially harmful exposures to occur. In the United States, women generally enter the Army as full-time workers sometime after completing secondary education, about 17-18 years of age. The breast tissue in these women is still developing and thus more susceptible to carcinogenic agents (25, 27, 43, 48).

This study focused on women between the ages of 18 and 45 and the organic chemical exposure that they experienced while holding occupations during active duty in the U.S. Army. The age span of the study population included most of the important milestones in breast tissue development, from the peak of breast tissue differentiation to menopause, and likely included a woman's first pregnancy if she became pregnant. The effect of the timing of organic chemical exposure on the occurrence of breast cancer was assessed by using summary measures of organic chemical exposure within time windows representing specific stages of breast tissue development and reproductive milestones for each member of the case-control study population.

METHODS

Study Population

The study population was selected from a cohort of women who served on active duty in the U.S. Army for at least one annual census from 1 January 1980 to 31 December 1996. Active duty refers to a member's status in the military and describes those who are legally obligated to serve (work) and support the military mission. The process for identifying the cases was described in Chapter 1. Briefly, 272 women were diagnosed with invasive breast cancer while on active duty between 1980 and 1996, and 98 of those cases had also completed a voluntary, self-administered HRA questionnaire. The control pool consisted of women who met the cohort definition and completed the same HRA instrument (N=~54,000). The controls were selected from the pool using incidence density sampling with replacement matched on risk age at a case-to-control ratio of 1:5. The HRA data were available from the TAIHOD through the Army Research Institute of Environmental Medicine (2, 3). This population was selected because the HRA provided information regarding several risk factors previously

associated with breast cancer that were otherwise unavailable, primarily age at menarche, age at birth of first child, family history of breast cancer, and history of tobacco and alcohol use. Due to restrictions on access to and use of personal health information, study members were not contacted. Encrypted SSNs were the only personal identifiers available, in order to protect the study members' identities.

Measures of Cumulative Exposure

A job exposure matrix with dimensions of MOS or job title and the airborne concentrations of the individual study chemicals and total organic chemical fractions by year was merged with the occupational history data for each study member. Before evaluating cumulative exposure for study members with exposure to more than one of the study chemicals, it was necessary to standardize the measures by converting the individual chemical measures to fractions of the current OEL (1). The OEL fractions were summed to obtain the total OEL fraction for each MOS-year combination. Cumulative exposure was calculated over the Army career of each woman by summing the products of the concentration of chemical (in parts per million) estimated for a particular MOS and the amount of time (in years) a woman held that MOS. Details of the procedure used to estimate exposure intensity and cumulative exposure are reported in Chapter 2. For the individual study chemicals, the units were ppm-yrs and for the total organic chemical exposure, the units were OEL fraction-yrs.

Because the JEM was constructed to yield annual concentration estimates for each chemical and MOS, cumulative exposures could be calculated for various ages, ranges of age, or ranges of years exposed (e.g., exposure within five years of risk age). Categories of cumulative exposure included "unexposed/exposed" and, within exposed, "low" and "high," depending upon the number of cases available in the analysis. Categorical cut-points for cumulative exposure groups were selected primarily at equal case number intervals to ensure an adequate distribution of cases within each exposure category. The fraction of the OEL (e.g., at 10% and 50% of the OEL) was considered for setting cumulative exposure cut-points, but was rejected due to unstable analysis. Due to the limited number of cases with exposure to the study chemicals, the final analysis was limited to the formaldehyde (Table 15).

Table 15. Demographic and Risk Factor Information for Cases and Their Matched Controls with Completed Health Risk Appraisal Questionnaires, 1980-1996

	Cases		Controls	
	N	Percent	N	Percent
Age in years at entry into Army				
18-24	60	61	287	59
25-34	33	34	174	36
35-44	3	3	18	4
45-54	2	2	5	1
Age in years at index year				
18-24	5	5	23	5
25-34	44	45	217	46
35-44	37	38	180	28
45-54	12	12	53	11
Race				
Black	42	43	221	46
White	44	45	217	45
Other	12	12	46	10
Family history of breast cancer				
No	66	69	421	88
Yes	30	31	55	12
Parity				
Nulliparous	35	36	194	40
Parous	63	64	290	60
Age at birth of first child				
≤ 25	39	40	201	42
26-30	17	17	61	13
≥ 31	7	7	28	6
Age in years at menarche				
≤ 12	44	45	250	52
13-14	43	44	181	38
≥ 15	11	11	49	10
Smoking history				
Never	60	62	280	58
Quit	20	21	95	20
Current	17	18	109	23
Current use of alcohol (drinks per week)				
None	65	68	290	61
1-6	25	26	164	35
7-13	4	4	14	3
≥ 14	1	1	6	1

a - Percentages rounded off

Breast Cancer Risk Factors

The risk factor information used in this study came from the HRA and was limited to those factors that have been recognized in the literature as significant contributors to breast cancer risk: age at menarche, age at birth of first child, parity, family history of breast cancer, race, and histories of tobacco and alcohol use. These potential

confounders were categorized using cut-points identified from the literature to define factors with the greatest effect on breast cancer risk.

Menarche. Age at menarche was divided into two categories: those through 12 years of age and those 13 years or older. An early age at menarche is thought to be a risk factor due to the increased exposure of breast tissue to developmental hormones (27, 28). The age at menarche to the age at first exposure was used to indicate the degree of breast tissue development at the age at first exposure.

Parity. Parity was categorized based on the response to the HRA question regarding the age of the women at the birth of her first child. Women responded with the value 0 or left the answer blank to indicate they were nulliparous.

Age at Birth of First Child. Parous women were divided into two categories: those who had their first child through the age of 25 years and those after age 25 years. The rate of breast tissue development slows and the risk for breast cancer begins to rise at around 25 years of age. To investigate the timing of first exposure with respect to parity status, three categorical variables were created:

Reference	Parous women with an age at first birth through 25 years of age (PARCAT0=1, for all others=0)
Category 1	Nulliparous women (PARCAT1=1, for all others=0)
Category 2	Parous women with an age at first birth after 25 years of age (PARCAT2=1, for all others=0)

Family History. Family history of breast cancer among sisters and mother is a very significant factor in a women's risk for breast cancer (9, 57, 61). In the risk models developed for this study, family history was treated as a dichotomous variable.

Race. This study population was relatively young, with a mean age of 35 years. Young black women, 20-40 years of age, are reported to have a higher incidence of breast cancer than white women and women of other races of the same age. From age 40 and older, white women have a higher incidence rate (59). Race was categorized into two categories, black women and all others.

Smoking Histories. Histories of smoking and alcohol consumption were reported in the HRA as continuous variables: number of cigarettes and drinks per week. Smoking was also categorized into three groups: "never smoked," "former smoker," and "active smoker." The time interval for years since quitting smoking was adjusted in the models to investigate the effect of quitting until the index age. The HRA database did not include information on the age at which smoking started or exposure to passive smoking, limiting the value of the smoking history variables. As reported by Lash and Aschengrau, using current and past smoking practices without reference to age and history of passive smoking underestimates the true risk associated with smoking and breast cancer (27).

Alcohol Consumption. Alcohol consumption was categorized based on findings that recent heavy drinking, defined as two or more drinks per day in the past

three to five years, was a significant risk factor for breast cancer (6, 32, 55, 57). The categories were "abstainer," "less than six drinks per week," "seven to 13 drinks per week," and "14 or more drinks per week." These categories were evaluated over the entire period of the study as if the reported drinking level was constant over the study period and in time windows going backward five years from the risk age.

Analysis

Conditional logistic regression was used to estimate relative odds ratios (OR) and their 95% confidence intervals, adjusted for potential confounders using SAS version 6.04 (SAS Institute, Cary, NC). Correlation coefficients were obtained between all variables in the model to identify and prevent using correlated measures in the same model. Measures of cumulative exposure were calculated up to the risk age in the full model, with limits based on the time window being investigated. The measures of cumulative exposure used included all years in the Army, from entry until 30 years of age (i.e., age at which the rate of breast tissue development has begun to decrease), from entry until age 35 (i.e., age at which breast tissue development ceases), and from entry until age 40 (i.e., age at which the menopause process begins). Cumulative exposure was expressed in the model as categorical or continuous variables. The full model was:

$$\text{Logit } P(X) = a + \beta_1 EXP + \beta_2 FH + \beta_3 RACE + \beta_4 PARITY + \beta_5 SMOKE \qquad (7)$$

where:

EXP =	Exposure Model 1:	unexposed, low, and high as categorical variables. The cut-point for low and high was selected to obtain an equal number of exposed cases.
	Exposure Model 2:	unexposed=0 and exposed=1
	Exposure Model 3:	a 3-level score using the cut-points in model 1, in which the unexposed were assigned 0, the low exposed 1, and the high exposure group was assigned a value of 2
FH =	Family history, where yes=1 and no=0 (reference)	
RACE =	Black women=1 and women of other races=0 (reference)	
PARITY =	Nulliparous=1 and parous=0 (reference)	
SMOKE =	Ever smoked=1 and never smoked=0 (reference)	

To investigate the effect of organic chemicals as late-stage tumor promoters, models were constructed that limited the calculation of cumulative exposure to the five years prior to the risk age using the exposure variables as defined above. To investigate the effect of the study chemicals with respect to parity status, a series of interaction terms (PAREXP) were created by combining parity status and the measures of exposure:

PAREXP0 = PARCAT0*EXP (first birth through 25 years of age)

PAREXP1 = PARCAT1*EXP (nulliparous)

PAREXP2 = PARCAT2*EXP (first birth after 25 years of age)

where EXP represents unexposed=0 and exposed=1, the exposure definitions used in model 2, Equation 7.

RESULTS

Study Population Description

Age. As shown in Table 6, the study population had similar distributions of age at entry into the Army and risk age when compared to the cohort population. Ninety-nine percent of the case and controls were younger than 45 years of age and were considered premenopausal.

Age at Menarche. Forty-five percent of the cases and 52% of the controls were 12 years of age or younger at menarche. These findings were similar to those reported in previous breast cancer risk studies of women younger than 45 years of age in which 50%-56% were 12 years or younger at menarche (8, 61), and in a study of breast cancer risk among middle-aged women in which 47% were 12 years or younger at menarche (17).

Family History of Breast Cancer. Thirty-one percent of the cases reported a family history of breast cancer, more than twice the number of controls (31% vs. 12%).

Parity. Fewer cases were nulliparous than the controls (36% vs. 40%).

Age at Birth of First Child. The percentage of women who had their first child after age 30 was about the same for cases (11%) and controls (10%). A higher percentage of the controls (69%) had their first children before age 26 than the cases (62%).

Smoking History. The percentages of women who never smoked in the cases (62%) and controls (58%) compared favorably with those reported in a cohort study of younger women (56%) (8).

Alcohol Use. The percentage of abstainers was 68% for cases and 61% for controls.

Conditional Logistic Models

Study Chemicals. The only study chemical with a sufficient number of exposed cases for the analysis was formaldehyde (Table 15). Formaldehyde was the only organic chemical with a majority of its estimates near the occupational exposure limit. It thus accounted for a majority of the total organic chemical fraction, which measured exposure as a fraction of its occupational exposure limit. Using this measure was considered to be a surrogate for formaldehyde exposure, and so it was dropped from

further analysis. All results reported in the remainder of the paper are limited to the analysis of cumulative exposure to formaldehyde.

Confounding Covariates. Women with a family history of breast cancer had the highest risk for breast cancer, although the risk decreased as risk age increased. The odds ratio for family history was 3.6 for all women in the study (Table 16). When the analysis was stratified on risk age, the odds ratio for women 35 years and younger was 12 (95% CI=4.6-33) and 1.8 (95% CI=0.8-3.8) for women older than 35 years (Table 17). Race and smoking history were not significantly associated with breast cancer in any of the models, but were retained for comparison with other studies. Alcohol history was not included in the models because the reported level of drinking was much lower than expected, and only one case and six controls were reported to be heavy alcohol users (Table 16).

Table 16. Results of Three Different Formaldehyde Exposure Models of Breast Cancer Risk. Exposure Assessed for All Years Prior to Risk Age

Model	Exposure Group	No. of cases	OR[a]	95%CI[b]
1	Reference – Unexposed	70	1.0	
	$\le$ 0.23 ppm-yrs[c]	14	1.2	0.6-2.4
	> 0.23 ppm-yrs	14	1.7	0.9-3.3
2	Exposed	28	1.4	0.9-2.4
3	3-level score[d]	28	1.4	0.9-2.3
Potential confounders[e]				
Family history				
Reference - No		68	1.0	
Yes		30	3.6[f]	2.1-6.1
Parity status				
Reference - parous		63	1.0	
Nulliparous		35	0.9	0.5-1.6
Smoking				
Reference - never		61	1.0	
Ever smoked		37	0.8	0.5-1.3
Race				
Reference - other		52	1.0	
Black women		44	0.8	0.5-1.4

a - Odds ratio, adjusted for family history, race, parity, and smoking history
b - 95% confidence interval
c - Parts per million years
d - Unexposed = 0, low exposure group = 1, high exposure group = 2
e - Each of the three exposure models included these potential confounders. Results were similar in all models; results from Model 1 are shown.
f - $p < 0.05$

Cumulative Exposure. The adjusted odds ratio for the study population indicated a nonsignificant increase in risk for all formaldehyde cumulative exposure variables in the three models (Table 16). When cumulative exposure was categorized by unexposed, low, and high (Model 1), the adjusted odds ratios increased with each exposure group, from 1.2 (95% CI=0.6-2.4) in the low exposure group to 1.7 (95% CI=0.9-3.3) in the high exposure group. To investigate the risk of breast cancer among women with the most active breast tissue, the study population was divided at a risk age of 35 years. The adjusted odds ratios for the association between breast cancer and

the exposure variables declined with increasing age, consistent with decreasing breast tissue development activity. Women 35 years and younger had an adjusted odds ratio of 2.2 (95% CI=0.7-6.9) in the highest exposure group. This was higher than the same exposure group for women older than 35 years (OR=1.3, 95% CI=0.8-3.2) (Table 17). Exposure could not be evaluated in other biological time windows due to an insufficient number of cases.

Table 17. Results of Three Different Formaldehyde Exposure Models of Breast Cancer Risk. Exposure Assessed for Risk Ages Through Age 35 and Greater Than Age 35

		< 35 years old			**> 35 years old**		
Model	**Exposure Group**	**No. of cases**	**OR[a]**	**95% CI[b]**	**No. of cases**	**OR**	**95% CI**
1	Unexposed	37	1.0		33	1.0	
	Lo - ≤ 0.23 ppm-yrs[c]	5	1.4	0.4-4.9	9	1.2	0.6-2.4
	Hi - > 0.23 ppm-yrs	7	2.2	0.7-6.9	7	1.3	0.8-3.2
2	Exposed	12	1.8	0.7-4.4	16	1.2	0.6-2.4
3	3-level score[d]	12	2.2	0.6-7.4	16	1.3	0.8-2.3
Potential confounders[e]							
Family history							
Reference - No		30	1.0		38	1.0	
Yes		19	12.0[f]	4.6-33	11	1.8	0.8-3.8
Parity status							
Reference - parous		16	1.0		19	1.0	
Nulliparous		33	1.0	0.4-1.9	30	1.3	0.7-2.6
Smoking							
Reference - never		35	1.0		26	1.0	
Ever smoked		14	0.5	0.2-1.2	23	1.0	0.5-1.8
Race							
Reference - other		21	1.0		33	1.0	
Black women		28	0.9	0.4-1.9	16	0.6	0.3-1.2

a - Odds ratio, adjusted for family history, race, parity, and smoking
b - 95% confidence interval
c - Parts per million years
d - Unexposed group = 0, low exposure group = 1, high exposure group = 2
e - Each of the three exposure models included these potential confounders. Results were similar in all models; results from Model 1 are shown.
f - $p < 0.05$

When exposure was limited to five years prior to risk age, the adjusted odds ratios increased for formaldehyde in Model 3 (Table 18). When exposure was limited to the five years prior to the risk age, the odds ratio for the highest exposed group was significantly elevated for women 35 years of age and younger (OR=3.4, 95% CI=1.0-9.1), an almost three-fold increase over the same exposure group in women older than 35 years (Table 19).

Table 18. Results of Three Different Formaldehyde Exposure Models of Breast Cancer Risk. Exposure Limited to the Five Years Prior to Risk Age

Model	Exposure Group	No. of cases	OR [a]	95%CI [b]
1	Reference – Unexposed	75	1.0	
	Lo- ≤ 0.1 ppm-yrs [c]	10	1.2	0.6-2.4
	Hi- > 0.1 ppm-yrs	13	1.8	0.9-3.7
2	Reference – Unexposed	75	1.0	
	Exposed	23	1.4	0.8-2.4
3	3-level score [d]	23	4.5	0.9-23
Potential confounders [e]				
Family history				
Reference – No		68	1.0	
Yes		30	3.6 [f]	2.1-6.1
Parity status				
Reference – parous		63	1.0	
Nulliparous		35	0.9	0.5-1.6
Smoking				
Reference – never		61	1.0	
Ever smoked		37	0.8	0.5-1.3
Race				
Reference - other		52	1.0	
Black women		44	0.8	0.5-1.4

a - Odds ratio
b - 95% confidence interval
c - Parts per million years
d - Unexposed = 0, low exposure group = 1, high exposure group = 2
e - Each of the three exposure models included these potential confounders. Results were similar in all models; results from Model 1 are shown.
f - $p < 0.05$

Table 19. Results of Three Different Formaldehyde Exposure Models of Breast Cancer Risk. Exposure Limited to the Five Years Prior to Risk Age Through Age 35 and Greater Than Age 35

		< 35 years old			> 35 years old		
Model	**Exposure Group**	**No. of cases**	**OR[a]**	**95% CI[b]**	**No. of cases**	**OR**	**95% CI**
1	Unexposed	37	1.0		38	1.0	
	Lo - ≤ 0.23 ppm-yrs[c]	4	1.2	0.2-3.7	6	1.1	0.4-2.8
	Hi - > 0.23 ppm-yrs	8	3.4[d]	1.0-9.1	5	1.2	0.4-3.3
2	Exposed	12	1.9	0.8-4.5	11	1.1	0.5-2.4
3	3-level score[d]	12	6.5	0.7-62	11	1.7	0.1-34
Potential confounders[e]							
Family history							
Reference - No		30	1.0		38	1.0	
Yes		19	12.0[d]	4.6-33	11	1.8	0.8-3.8
Parity status							
Reference - parous		16	1.0		19	1.0	
Nulliparous		33	1.0	0.4-1.9	30	1.3	0.7-2.6
Smoking							
Reference - never		35	1.0		26	1.0	
Ever smoked		14	0.5	0.2-1.2	23	1.0	0.5-1.8
Race							
Reference - other		21	1.0		33	1.0	
Black women		28	0.9	0.4-1.9	16	0.6	0.3-1.2

a - Odds ratio, adjusted for family history, race, parity, and smoking
b - 95% confidence interval
c - Parts per million-years
d - $p < 0.05$
e - Unexposed group = 0, low exposure group = 1, high exposure group = 2
f - Each of the three exposure models included these potential confounders. Results were similar in all models; results from Model 1 are shown.

Age at Birth of First Child

To investigate whether delaying first childbirth increased breast cancer risk in women exposed to formaldehyde, two new variables were created. Age at first birth was dichotomized around age 25, the midpoint between the age at which first birth is significantly protective against breast cancer (age 20), and the age at which first birth begins to significantly increase a woman's risk of breast cancer (age 30). Due to the low number of exposed cases, Model 2 was used in the analysis. Construction of the interaction term was described earlier.

When parity status is used in a model as a dichotomous variable in the main effects model, the adjusted odds ratio for nulliparous women compared to parous women was nonsignificantly lower than 1 (Table 16). When parity is used in the same model as three dummy variables, the adjusted odds ratio for nulliparous women was less than 1 and later parous was 1.3 (95% CI=0.7-2.4) (Table 20).

Table 20. Results of Model for Breast Cancer Risk Including Dichotomous Exposure Variable (Model 2) and Three Levels of Parity. Exposure Time Period All Years in Army up to Risk Age

	No. of cases	OR[a]	95% CI[b]
Exposure Group			
Reference - Unexposed	70	1.0	
Exposed	28	1.4	0.9-2.4
Family history			
Reference - No	68	1.0	
Yes	30	3.6[c]	2.1-6.1
Parity status and age at birth of first child			
Reference[d]	39	1.0	
Nulliparous	35	0.9	0.5-1.5
Late first birth[e]	24	1.3	0.7-2.4
Smoking			
Reference - never	61	1.0	
Ever smoked	37	0.8	0.5-1.3
Race			
Reference - other	52	1.0	
Black women	44	0.8	0.5-1.4

a - Odds ratio
b - 95% confidence interval
c - $p < 0.05$
d - First birth through 25 years of age
e - First birth after 25 years of age

Age at Birth of First Child and Exposure Interaction

Using the dichotomous exposure variable (exposed/unexposed) from Model 2 and the three-level parity status variable, dummy interaction terms were created. When the interaction terms were introduced into the main model to investigate potential effect modification, the adjusted odds ratios for exposure and late first birth were lower, indicating effect modification (Table 21). The resulting adjusted odds ratios for exposed nulliparous women and the later parous women exposed to formaldehyde were reduced. When the interaction term representing the later parous women was used without the main effects of parity or exposure, the adjusted odds ratio was 3.4 (95% CI=1.4-8.2) (Table 22). This means that women with any formaldehyde exposure and their first birth after age 25 were 3.2 times more likely to develop breast cancer as women with no formaldehyde exposure and/or first birth before age 25.

Table 21. Results of Model for Breast Cancer Risk Including Dichotomous Exposure Variable (Model 2), Two Levels of Parity, and an Interaction Term. Exposure Time Period All Years in Army up to Risk Age

	No. of cases	OR[a]	95% CI[b]
Exposure Group			
Reference – Unexposed	70	1.0	
Exposed	28	1.0	0.5-1.9
Parity status			
Reference[c]	74	1.0	
Late first birth[d]	24	0.9	0.5-1.6
Interaction			
Reference[d]	87	1.0	
Late first birth and exposed	11	3.6[e]	1.2-11.0
Family history			
Reference – No	68	1.0	
Yes	30	3.7[e]	2.2-6.4
Smoking			
Reference – never	61	1.0	
Ever smoked	37	0.8	0.5-1.3
Race			
Reference – other	52	1.0	
Black women	44	0.8	0.5-1.43

a - Odds ratio, adjusted for family history, race, and smoking history
b - 95% confidence interval
c - First birth through 25 years of age and nulliparous
d - First birth through 25 years of age, nulliparous, and first birth after age 25 years with no history of exposure
e - $p < 0.05$

Table 22. Results of Model for Breast Cancer Risk Including Only the Interaction Term Between Exposure (Model 2) and Parity. Exposure Time Period All Years in Army up to Risk Age

	No. of cases	OR[a]	95% CI[b]
Interaction of Parity and Exposure			
Reference[c]	87	1.0	
Late first birth and exposed	11	3.2[d]	1.5-6.9

a - Odds ratio, adjusted for family history, race, and smoking history
b - 95% confidence interval
c - First birth through 25 years of age, nulliparous, and first birth after age 25 years with no history of exposure
d - $p < 0.05$

CONCLUSION AND RECOMMENDATIONS

This study found that women who delayed the birth of their first child after age 25 years and had occupational exposure to formaldehyde before their first pregnancy or at anytime while in the Army had a 3.2 times increased risk for breast cancer when compared to nulliparous and women who had their first child at a younger age. This finding is consistent with the study hypothesis that exposure to formaldehyde during a developmental stage when breast tissue is proliferating increases the risk for breast cancer.

This study found that 31% of the cases reported a positive family history for breast cancer, more than two-fold increase over the controls. Of the literature available

for premenopausal women, two studies reported a two-fold increase (8, 58), and one study reported a range of 31%-32% positive history of having a primary relative with invasive breast cancer (61). This study also found that a positive family history of breast cancer did not have a uniform effect over all ages. As age increased, the family history odds ratio decreased, suggesting diminished influence of a positive family history of breast cancer on breast cancer risk due to inherited traits as a woman ages. In a relatively young population, it was expected that younger women would be less likely to report that she had a sister or mother with breast cancer than older women. In the two studies cited above, the incidence of breast cancer was based on primary relatives, mother or sisters. The Army HRA did not use as specific a definition because the question was worded "How many family members have had breast cancer"? This may account for the difference reported by the Army and the other two studies. It may also introduce some bias, because women with breast cancer are more likely to be aware of the occurrence throughout the extended family, increasing the percentage reported among the cases. Misclassification of family history, such as reporting an aunt as a primary relative with breast cancer, would bias the true risk towards the null and underestimate the odds ratio. An underestimation of the risk does not appear to have occurred in this study, because the odds ratio for family history in this study was higher than comparable studies of breast cancer (8, 58).

The other potential confounders, race, smoking history, and alcohol consumption, typically reported to be associated with breast cancer risk did not appear to be risk factors in this population. A history of current alcohol use was not used in the model, because the abstainer percentage appeared to be unreasonably high, and there was only one case and six controls in the group that was reported in the literature as having an exposure associated with increased risk (6, 32, 55, 57). This may be partially explained by a combination of increased alcohol abuse prevention education and increased intolerance for alcohol abuse by the Army. While the education program may lead to lower drinking rates, it is also possible that soldiers are underreporting true alcohol consumption through concern about consequences that may befall them if their superiors would deem their alcohol consumption excessive.

Based on the model of breast tissue development, it was decided that the timing of first exposure to formaldehyde and parity status should be investigated. It was hypothesized that organic chemical exposure occurring while breast tissue was in a proliferative stage might present more risk than exposure that occurred when the tissue had completed development. In this study, it was found that parous women who delayed the birth of their first child until after age 25 and had an occupational history of exposure to formaldehyde had a more than three-fold increase in breast cancer risk when compared to all other women in the study. The ideal design would stratify on the age of the woman at the birth of first child (i.e., < 20, 20-30, and > 30) in combination with age at first exposure to formaldehyde. This would require many more than the 23 parous cases with occupational exposure to formaldehyde available in this study.

It has been proposed and observed that some breast cancers are very aggressive, while others may take years or decades to advance (24). Yet, in epidemiologic studies, all are grouped into a single outcome of breast cancer. For

example, the Surveillance, Epidemiology, and Endpoints Report (59) shows invasive breast cancer incidence and mortality as a single disease based on the pathology diagnosis code. Several researchers, including Spratt (53, 54) and Winchester (62), have proposed that breast cancer maybe at least two separate diseases, with a more aggressive and rapidly growing type occurring in younger women. However, because breast cancer in young women (i.e., less than 35 years) is very rare, it may be overshadowed by the high incidence of breast cancer in older, menopausal women. Because this study was primarily one of premenopausal women, the investigation of breast cancer among young women was possible. A study with more cases in the older and younger groups would improve the evaluation.

Some of the estimates of this study were imprecise due to limitations of the available data. The exposure estimation used nine years of measurement data to provide estimates for a 37-year period (the full time period covered by women employed between 1980-1996) that included many factors likely to affect exposure, such as the regulation of occupational exposures and the introduction of women into the industrial shops of the Army. The estimates of exposure intensities used for the job exposure matrix were within the range of levels reported in the literature. However, the estimates may be too low for the years when women were employed prior to 1980. When the models limited cumulative exposure to the most recent five years, the estimates of exposure intensity in the job exposure matrix were generally from the same years as the measurements from the air-sampling database.

Occupational exposure to some organic compounds and the risk of breast cancer have been the subject of two papers, both indicating a positive association, but lacking any method to quantify exposure beyond dichotomous variables (18, 41). Breast cancer mechanisms proposing that organic solvents promote cancer in a manner similar to those for alcohol (16, 19, 22, 26, 57) have not been investigated due to insufficient occupational histories and exposure information, especially in the United States. This is the first study to use annual occupational histories and uniformly collected exposure data to quantitatively estimate risk of breast cancer associated with several organic chemicals in a large and diverse occupational cohort of women.

CHAPTER 4: CONCLUSIONS AND RECOMMENDATIONS

This is the first breast cancer study to use quantitative measures of cumulative exposure for occupational chemicals to assess the risk of breast cancer, especially in young women. The primary findings were:

(1) Women in jobs with occupational formaldehyde exposure who delayed the birth of their first child until after 25 years of age experienced a significantly increased risk for breast cancer compared to all other women in the study, and

(2) A family history of breast cancer was associated with a significantly increased risk of breast cancer among young women (i.e., 35 years and under).

STUDY RECOMMENDATIONS

Based on these findings, we make the following recommendations:

A. Workplaces that employ young women and use formaldehyde should find less toxic substitutes for formaldehyde or install engineering controls to reduce worker exposure. Because this study did not evaluate breast cancer risks for older women or formaldehyde exposure for men, protection for all workers should be evaluated.

B. Women who work in jobs with frequent formaldehyde exposure should be screened for breast cancer at earlier ages and receive targeted awareness training.

C. Worker exposure profiles are needed to improve exposure estimation and dose-response relationship for disease. While there is a mechanism that might explain how formaldehyde acts as a breast-tissue carcinogen, these women might also be exposed to other chemicals or combinations of chemicals that truly increase their risk.

D. Women with a familial history of breast cancer should be screened earlier and receive targeted awareness training. Working women with a history of breast cancer in their mother or sister(s) need to begin regular screening as soon as they are aware of their family history. As seen in this study, this may occur much earlier than the recommended 40 years of age. The strongest association between breast cancer and family history was observed in the youngest subset of the study population and was significantly elevated for the case-control population.

E. Improve the histopathological diagnoses for breast cancer to distinguish between more aggressive forms of breast cancers with a short latency, found mostly in young women, from those with longer latency. The methods used to diagnose invasive breast cancer need to be refined to differentiate breast cancers by their rate of growth. Until breast cancer is recognized as having more than one disease process, the ability to investigate special populations will be limited and those results misleading.

F. Improve record archiving system for the military. Sixty percent of the records reviewed in this study were incomplete or missing. The Army has policies and procedures for archiving the health record for each member when they leave the service to provide health information for future health claims, not to facilitate data abstraction for epidemiologic research. Military health records are the property of the U.S. government and must be submitted for storage at the end of service. The original plan for the study was to review more than 1,200 health records for cases and controls to obtain risk factor information. The data abstraction was labor intensive and expensive and added little to the quality of the study. Of the 237 cases originally identified through the hospitalization database in the TAIHOD, only 26 had complete records in the archive, 12 were missing significant parts of the case history, 22 were still on active duty or in the Army Reserves at the end of 1996, and 177 records were missing. An analysis of cost to review 1,200 health records to do a complete data abstraction for breast cancer risk factors alone found that it would take 500 person-hours and a cost of $14,400 due to the poor organization and condition of the records. The use of archived records for health studies is not recommended where the responsibility for retiring the records rests solely with the individual and the completeness of the records cannot be ascertained beforehand.

G. Establish a case-control data warehouse for breast cancer (and other selected diseases) with complete health and occupational histories including quantitative workplaces exposure. The cost of obtaining risk factor information is a major concern of health researchers. To improve the quality of the demographic and risk factor information, a cancer case-control registry should be established at the Department of Defense (DoD). For each case identified through the DoD tumor registry, a set of controls (e.g., 10-20 service members) should be randomly selected, matching age at diagnosis. The cases and controls would receive comprehensive physical exams and a complete work history under the guidance of the local occupational health office. To protect the privacy of the cases and controls, a unique identifier would be used in place of the SSN. Industrial hygiene and environmental data from the DoD occupational database would be linked to each case and control by job title and dates of employment. DoD, through the Army, has planned a system similar to the one constructed in this study, which used exposure profiles to create similar exposure groups (SEGs). DoD could provide the case-control data in database, spreadsheet, or text format to meet the needs of researchers at a reasonable cost. The researchers would get a high-quality data pool to test their theories, and the DoD would benefit from high-quality research in return.

FURTHER STUDY

This work highlights the need for additional research efforts in the following areas:

A. Increase the study period from 1997–1999, and obtain more cases with data on alcohol consumption. More cases will provide increased power for investigating other potential confounders, such as race.

B. Obtain hard copy industrial hygiene reports prior to 1989 to improve and validate exposure estimation. The Army maintains a microfiche archive of industrial hygiene surveys that must be searched by on-site technicians using keywords. By focusing on formaldehyde and other selected chemicals, past workplace exposure intensities can be used to improve the estimates of exposure used in this study.

C. Look at other frequently monitored chemicals suspected to be breast cancer carcinogens (e.g., lead) using the job exposure matrices and conditional logistic regression programs developed for this study. Lead has been mentioned in several studies as a potential breast carcinogen. Lead is highly regulated, increasing the likelihood that multiple air samples were taken for many MOSs and work locations.

The world has seen many changes over the last 50 years that have increased the difficulty in isolating the causes of breast cancer. Women who live in industrialized regions have experienced changes in their reproductive patterns to accommodate their new lifestyle. Millions of new chemicals have been introduced into the water, air, and food supplies. The complexity of the endocrine system makes it difficult to observe any mechanism in the isolation of the research laboratory and apply it to the human system. On the positive side, breast cancer research has expanded to include the mapping and identification of human genes, prophylactic drug therapy, drugs that starve the tumor and reduce toxicity for the patient, and risk reduction through dietary changes. Research into environmental factors for breast cancer provides a measure of success at the human level for interventions developed through cooperation with other research disciplines.

REFERENCES

1. American Conference of Governmental Industrial Hygienists. *1997 TLVs and BEIs*. American Conference of Governmental Industrial Hygienists, Cincinnati, OH, 1997.

2. Amoroso, P. J., W. G. Swartz, F. A. Hoin, and M. M. Yore. *Total Army Injury and Health Outcomes Database: Description and Capabilities*. Natick, MA: U.S. Army Research Institute of Environmental Medicine. Technical Note TN97-2, February 6, 1997.

3. Amoroso, P. J., M. M. Yore, B. Weyandt, and B. H. Jones. Chapter 8. Total Army Injury and Health Outcomes Database: a model comprehensive research database. *Mil Med*. 164(8 Suppl): 1-36, 1999.

4. Barbone, F., R. Filiberti, S. Franceschi, R. Talamini, E. Conti, M. Montella, and C. L. Vecchia. Socioeconomic status, migration and the risk of breast cancer in Italy. *Int J Epidemiol*. 25(3): 479-487, 1996.

5. Blank KR. BRCA-1: The Breast-Ovary Cancer Gene: Epidemiology and Implications of Genetic Testing [internet press release]. Oncolink: University of Pennsylvania Cancer Center web site. Available at: http://oncolink.upenn.edu/causeprevent/genetics/brca1/blank.html. Accessed 1996.

6. Bowlin, S. J., M. C. Leske, A. Varma, P. Nasca, A. Weinstein, and L. Caplan. Breast cancer risk and alcohol consumption: results from a large case-control study. *Int J Epidemiol*. 26(5): 915-923, 1997.

7. Brinton, L. A., J. Benichou, M. D. Gammon, D. R. Brogan, R. Coates, and J. B. Schoenberg. Ethnicity and variation in breast cancer incidence. *Int J Cancer*. 73(3): 349-355, 1997.

8. Brinton, L. A., J. R. Daling, J. M. Liff, J. B. Schoenberg, K. E. Malone, J. L. Stanford, R. J. Coates, M. D. Gammon, L. Hanson, and R. N. Hoover. Oral contraceptives and breast cancer risk among younger women. *J Natl Cancer Inst*. 87(11): 827-835, 1995.

9. Cannon-Albright, L. A., and M. H. Skolnick. The genetics of familial breast cancer. *Semin Oncol*. 23(1Suppl 2): 1-5, 1996.

10. Coogan, P. F., R. W. Clapp, P. A. Newcomb, R. Mittendorf, G. Bogdan, J. A. Baron, and M. P. Longnecker. Variation in female breast cancer risk by occupation. *Am J Ind Med*. 30: 430-437, 1996.

11. Davis, D. L., and S. M. Sieber. Hormones, hormone metabolism, environment, and breast cancer: A workshop of the National Action Plan on Breast Cancer's Etiology Working Group. *Environ Health Perspect*. 105(Suppl 3): 557, 1997.

12. Davis, D. L., N. T. Telang, M. P. Osborne, and H. L. Bradlow. Medical hypothesis: bifunctional genetic-hormonal pathways to breast cancer. *Environ Health Perspect*. 105(Suppl 3): 571-576, 1997.

13. Department of the Army. *Industrial Hygiene Program*. Washington, D.C. DA PAM 40-503, January 98.

14. Department of the Army, Headquarters. *Military Occupational Classification and Structure Update 6*. Washington, D.C. AR 611-1, 1995.

15. Esmen, N. Retrospective industrial hygiene surveys. *Am Ind Hyg Assoc J*. 40: 58-65, 1979.

16. Goldberg, M. S., and F. Labrèche. Occupational risk factors for female breast cancer: a review. *Occup Environ Med*. 53: 145-156, 1996.

17. Habel, L. A., J. L. Stanford, T. L. Vaughan, M. A. Rossing, L. F. Voigt, N. S. Weiss, and J. R. Daling. Occupation and breast cancer risk in middle-aged women. *J Occup Environ Med*. 37(3): 349-356, 1995.

18. Hansen, J. Breast cancer risk among relatively young women employed in solvent-using industries. *Am J Ind Med.* 36(1): 43-47, 1999.

19. Harvey, E. B., C. Schairer, L. A. Brinton, R. N. Hoover, and J. F. J. Fraument. Alcohol consumption and breast cancer. *J Natl Cancer Inst.* 78(4): 657-661, 1987.

20. Holness, D. L., and J. R. Nethercrott. Health status of funeral service workers exposed to formaldehyde. *Arch Environ Health.* 44(4): 222-228, 1989.

21. Ijaduola, T. G., and E. B. Smith. Pattern of breast cancer among white-American, African-American, and nonimmigrant west-African women. *J Natl Med Assoc.* 90(9): 547-551, 1998.

22. Katsouyanni, K., A. Trichopoulou, S. Stuver, S. Vassilaros, Y. Papadiamantis, N. Bournas, N. Skarpou, N. Mueller, and D. Trichopoulos. Ethanol and breast cancer: an association that may be both confounded and causal. *Int J Cancer.* 58(3): 356-361, 1994.

23. Kilburn, K. H., B. C. Seidman, and R. Warshaw. Neurobehavioral and respiratory symptoms of formaldehyde and xylene exposure in histology technicians. *Arch Environ Health.* 40(4): 229-233, 1985.

24. Kolata, G. New view sees breast cancer as 3 diseases. *New York Times.* April 1, 1997.

25. Kuller, L. H. The etiology of breast cancer - from epidemiology to prevention. *Public Health Rev.* 23: 157-213, 1995.

26. LaBrèche, F. P., and M. S. Golberg. Exposure to organic solvents and breast cancer in women: a hypothesis. *Am J Ind Med.* 32: 1-14, 1997.

27. Lash, T. L., and A. Aschengrau. Active and passive smoking and the occurrence of breast cancer. *Am J Epidemiol.* 149(1): 5-12, 1999.

28. Lipworth, L. Epidemiology of breast cancer. *Eur J Cancer Prev.* 4: 7-30, 1995.

29. Liu, L., D. Deapen, and L. Bernstein. Socioeconomic status and cancers of the female breast and reproductive organs: a comparison across racial/ethnic populations in Los Angeles County, California (United States). *Cancer Causes Control.* 9(4): 369-380, 1998.

30. Longnecker, M. P. Alcohol consumption and risk of cancer in humans: an overview. *Alcohol.* 12(2): 87-96, 1995.

31. Longnecker, M. P., P. A. Newcomb, R. Mittendorf, E. R. Greenberg, R. W. Clapp, G. F. Bogdan, J. Baron, B. MacMahon, and W. C. Willett. Risk of breast cancer in relation to lifetime alcohol consumption. *J Natl Cancer Inst.* 87(12): 923-929, 1995.

32. Longnecker, M. P., A. Paganini-Hill, and R. K. Ross. Lifetime alcohol consumption and breast cancer risk among postmenopausal women in Los Angeles. *Cancer Epidemiol Biomarkers Prev.* 4(7): 721-725, 1995.

33. Miller, B. A., L. N. Kolonel, L. Berstein, J. L. Young, Jr., G. M. Swanson, D. West, C. R. Key, J. M. Liff, C. S. Glover, G. A. Alexander. *Racial/ethnic patterns of cancer in the United States 1988-1992.* Bethesda, MD: National Cancer Institute. NIH Pub. No. 96-4101, 1996.

34. Morgan, D. A. *Occupational Health Management Information System (OHMIS): Health Hazard Information Module Version 2.2 (HHIM).* Aberdeen MD: Department of the Army. Software manual 1997.

35. Morgan, D. A. *Occupational Health Management Information System (OHMIS): Health Hazard Information Module Version 2.2 (HHIM).* Aberdeen MD: Department of the Army. Software manual 1997.

36. Women's Bureau, U.S. Department of Labor. *Nontraditional occupations for women in 1997.* Available at: http://www.dol.gov/dol/wb/public/wb_pubs/nontra97.htm.

37. Murrell, T. G. C. Epidemiological and biochemical support for a theory on the cause and prevention of breast cancer. *Med Hypotheses.* 36: 389-396, 1991.

38. National Cancer Institute. *Prevention of Breast Cancer*. Bethesda: National Cancer Institute. 1997.

39. National Cancer Institute. *SEER Cancer Statistics Review 1973-1994*. Bethesda: National Cancer Institute 1996.

40. Nayebzadeh, A., and A. Dufresne. Evaluation of exposure to methyl methacrylate among dental laboratory technicians. *Am Ind Hyg Assoc J*. 60(5): 625-628, 1999.

41. Petralia, S. A., W. H. Chow, J. McLaughlin, F. Jin, Y. T. Gao, and M. Dosemeci. Occupational risk factors for breast cancer among women in Shanghai. *Am J Ind Med*. 34(5): 477-483, 1998.

42. Petralia, S. A., J. E. Vena, J. L. Freudenheim, J. R. Marshall, A. Michalek, J. Brasure, M. Swanson, and S. Graham. Breast cancer risk and lifetime occupational history: employment in professional and managerial occupations. *Occup Environ Med*. 55(1): 43-48, 1998.

43. Pike, M. C., D. V. Spicer, L. Dahmoush, and M. F. Press. Estrogens, progesterones, normal breast cell proliferation, and breast cancer risk. *Epidemiol Rev*. 15(1): 17-35, 1993.

44. Pollan, M., and P. Gustavsson. High-risk occupations for breast cancer in the Swedish female working population . *Am J Public Health*. 89(6): 875-881, 1999.

45. Post, W., H. Kromhout, D. Heederik, D. Noy, and R. S. Duijzentkunst. Semiquantitative estimates of exposure to methylene chloride and styrene: the influence of quantitative exposure data. *Appl Occup Environ Hyg*. 6(3): 197-204, 1991.

46. Rubin, C. H., C. A. Burnett, W. E. Halperin, and P. J. Seligman. Occupation as a risk identifier for breast cancer. *Am J Public Health*. 83: 1311-1315, 1993.

47. Russo, J., and I. H. Russo. Experimentally induced mammary tumors in rats. *Breast Cancer Res Treat*. 39: 7-20, 1996.

48. Russo, J., and I. H. Russo. The etiopathogenesis of breast cancer prevention. *Cancer Lett*. 90: 81-89, 1995.

49. Russo, J., and I. H. Russo. Toward a physiological approach to breast cancer prevention. *Cancer Epidemiol Biomarkers Prev*. 3: 353-364, 1994.

50. Schottenfield, D., and J. F. J. Fraumeni. *Cancer Epidemiology and Prevention* (2nd ed). New York: Oxford University Press, 1996.

51. Seixas, N. S., and H. Checkoway. Exposure assessment in industry specific retrospective occupational epidemiology studies. *Occup Environ Med*. 52: 625-633, 1995.

52. Smith, T. J., S. K. Hammond, and S. R. Woskie. Exposure assessment for epidemiology: characteristics of exposure. *Appl Occup Environ Hyg*. 6(6): 441-447, 1991.

53. Spratt, J. A., D. von Fournier, J. S. Spratt, and E. E. Weber. Decelerating growth and human breast cancer. *Cancer*. 71(6): 2013-2019, 1993.

54. Spratt, J. A., D. von Fournier, J. S. Spratt, and E. E. Weber. Mammographic assessment of human breast cancer growth and duration. *Cancer*. 71(6): 2020-2026, 1993.

55. Stampfer, M. J., G. A. Colditz, and W. C. Willett. Alcohol intake and risk of breast cancer. *Compr Ther*. 14(5): 8-15, 1988.

56. Stewart, P. A., H. Triolo, J. Zey, D. White, R. F. Herrick, R. Hornung, M. Dosemeci, and L. M. Pottern. Exposure assessment for a study of workers exposed to acrylonitrile. II. A computerized exposure assessment program. *Appl Occup Environ Hyg*. 10(8): 698-706, 1995.

57. Swanson, C. A., R. J. Coates, K. E. Malone, M. D. Gammon, J. B. Schoenberg, D. J. Brogran, M. McAdams, N. Potischman, R. N. Hoover, and L. A. Brinton. Alcohol consumption and breast cancer risk among women under age 45 years. *Epidemiol*. 8: 231-237, 1997.

58. Tavani, A., C. Braga, C. L. Vecchio, E. Negri, A. Russo, and S. Franceschi. Attributable risks for breast cancer in Italy: education, family history and reproductive and hormonal factors. *Int J Cancer.* 70: 159-163, 1997.

59. U.S. Department of Health and Human Services. *SEER Cancer Statistics Review.* Internet Report Bethesda: National Institutes of Health, 1997.

60. Vorherr, H. Endocrinology of breast cancer. *Maturitis.* 9: 113-122, 1987.

61. Weiss, H. A., L. A. Brinton, D. Brogan, R. J. Coates, M. D. Gammon, K. E. Malone, and J. B. Schoenberg. Epidemiology of *In Situ* and invasive breast cancer in women aged under 45. *Br J Cancer.* 73: 1298-1305, 1996.

62. Winchester, D. P., R. T. Osteen, and H. R. Menck. The National Cancer Data Base report on breast carcinoma characteristics and outcome in relation to age. *Cancer.* 78(8): 1838-1843, 1996.

APPENDIX A: PERSONNEL DATABASE IN THE TOTAL ARMY INJURY AND HEALTH OUTCOMES DATABASE (TAIHOD)

PURPOSE

To obtain demographic information and calculate person time for soldiers who served on active duty in the Army between 1980 and 1996 from the personnel database in the TAIHOD.

DESCRIPTION OF DATABASE

Overview

The Army collects information for each person on active duty at least quarterly, including sex, race, age, ethnic origin, pay grade, rank, primary and duty occupational specialty, dates of entry into active service, changes in pay grade, educational level, marital status, and unit location. This particular data set uses the annual census taken on 31 December of each year. To be included in the census, the person must be on active duty as of the census date. Persons who left active service prior to the census date are listed in a so-called "loss database" that includes the date of separation. The census database can be amended if:

1. the person was listed in the census taken the calendar year prior to separation, or
2. the person separated and re-enlisted in the same calendar year.

If a person entered and left the service within the same calendar year, they are listed in the loss file but have no demographic information in the census database. These people were excluded from the study.

Limitations

The software to collect the census data did not have any internal validity checks, thus a person may have been listed as a man one year and a woman the next. Specifically,

1. Military Occupational Specialty codes. While enlisted and warrant personnel have only one possible code for their record, officers have two possible codes: functional and branch codes. Branch codes are assigned based upon a person's qualifications and desires. Functional codes are assigned based upon specialized training or skills. Either code may be used as the first three characters of the occupational specialty code. For example, an industrial hygienist has a branch code for Preventive Medicine Services (67C) and a functional code of Environmental Science (72D). All persons had branch codes, but functional codes are not required unless the position requires them or the person has completed seven years on active duty. Optional coding schemes use the DOT,

Census, and DoD area and group codes, providing a more consistent assessment of the distribution of person time within occupational specialties.

2. Obsolete occupational codes. The qualifications required to operate specific equipment change with advances in technology. New codes are created and old codes are converted to meet these needs. Some occupational specialties are discontinued due to a lack of direct conversion to the new qualifications from the old code. To account for this, a review of obsolete and discontinued codes was conducted using conversion files from the Defense Manpower Data Center and Army Regulation AR-611 to find the closest current occupational code. Those with no direct link were listed as obsolete.
3. Gender. Some persons with multiple census entries did not have the same gender listed over the years. There is no other database that has a validated SSN and gender entry from which to correct the census files. Since this is a study of women, all conflicting entries were converted to women. This will conservatively increase the total person time, reducing any standardized incidence rates.

<u>Person-Time</u>

Person-time was calculated using the following scheme:

1. If a person had a pay entry base date prior to the calendar year of the census file and no entry in the date of separation field, they were assigned one year of person-time.
2. If a person had a pay entry base date within the calendar year of the census file and no entry in the date of separation field, they were assigned a fraction of the year (days of the year/365) of person-time.
3. If a person had a pay entry base date within the calendar year of the census file and an entry in the date of separation field, they were assigned a fraction of the year (days of the year/365) of person-time.
4. If a person had a pay entry date within the calendar year of the census file and an entry in the date of separation field, no person-time was assigned because the person entered and left the Army in the year.

APPENDIX B: OCCUPATIONAL CLASSIFICATION AND TASK PROFILE FOR LIGHT-WHEEL VEHICLE MECHANIC (MOS 63B)

OCCUPATIONAL CLASSIFICATION

A. Major Duties

The light-wheel vehicle mechanic supervises and performs unit maintenance and recovery operations on gasoline and diesel fueled light-wheel vehicles (prime movers designated as five tons or less and their associated trailers), and associated items; supervises unit maintenance and recovery operations on track and heavy-wheel vehicles, and on material handling equipment (MHE). Duties for MOS 63B at each skill level are:

1. MOSC 63B10. Maintains power assisted brake systems, wheel vehicle suspension systems, wheel vehicle/hub assemblies, wheel vehicle mechanical (manual) steering systems, wheel vehicle hydraulic (power) steering systems, and wheel vehicle crane/hoist/winch assemblies.
2. MOSC 63B20. Perform duties in preceding skill level, supervises lower grade soldiers, and provides technical guidance to the soldiers in the accomplishment of their duties.
3. MOSC 63B30. Performs duties in preceding skill levels, perform light-wheel vehicle mechanic duties, perform heavy-wheel vehicle mechanic (63S) duties, perform track vehicle mechanic (63Y) duties, supervises lower rank soldiers, and provides technical guidance to the soldiers in the accomplishment of their duties. Supervises unit maintenance on wheel and track vehicles, material handling equipment, power generation equipment and upkeep of hand and power tools. Perform battlefield damage assessment and repair. Supervises recovery operations.
4. MOSC 63B40. Performs duties in preceding skill levels, supervises lower grade soldiers and provides technical guidance to the soldiers in accomplishment of their duties.
5. MOSC 63B50. Performs duties in preceding skill levels, supervises lower grade soldiers and provides technical guidance to the soldiers in accomplishment of their duties.

B. Physical Demands Rating and Qualifications for Initial Award of MOS

1. A physical demands rate of very heavy – occasional lifting of 100 pounds and frequent lifting of 50 pounds.
2. A physical profile of 222222. This code is used to profile the physical capabilities of various body parts – physical capacity (stamina), upper and lower extremities, hearing, eyes, and psychiatric. A code of one is ideal and a code of two is slightly less than idea.
3. Normal color vision.

4. A minimum score of 90 in aptitude area for Motor Maintenance in the Armed Services Vocational Aptitude Battery.
5. Current equipment qualifications record for all types of equipment maintained.
6. Formal training (completion of 63B course) mandatory; or meet the civilian acquired skills criteria listed in AR 610-210.

C. Additional Skill Identifiers

1. H8 – Recovery Operations
2. P5 – Master Fitness Trainer
3. 2S – Battle Staff Operations (skill level 3 and above)
4. 4A – Reclassification Training

D. Related Civilian Occupations

1. DOT Classification
   a. Automobile mechanic – 620.261-010
   b. Diesel mechanic – 625.281-010
   c. Truck mechanic – 620.261-010
   d. Tire repairer – 750.681-010

2. Federal civil service classification
   a. Heavy mobile equipment mechanic – WG 5803
   b. Automotive mechanic – WG 5823

E. Physical Requirements and Standards of Grade

1. Physical requirements
   a. Occasionally lifts 230 pounds as part of a two-soldier team
   b. Occasionally lifts 150 lbs, carries ten feet, and climbs five feet as part of a two-soldier team
   c. Must possess normal color vision
   d. Frequently reads detailed technical manuals
   e. Must possess finger dexterity in both hands
   f. Frequently lifts 75 lbs and carries 50 feet

2. Standards of grade
   a. Light-wheel vehicle mechanic --- PFC to SGT
   b. Senior Mechanic --- SSG
   c. Motor Sergeant --- SSG
   d. Motor Sergeant --- SFC
   e. Senior Maintenance Supervisor --- MSG